General Strategies toward the Syntheses of Macrolide Antibiotics. The Total Syntheses of 6-Deoxyerythronolide B and Oleandolide

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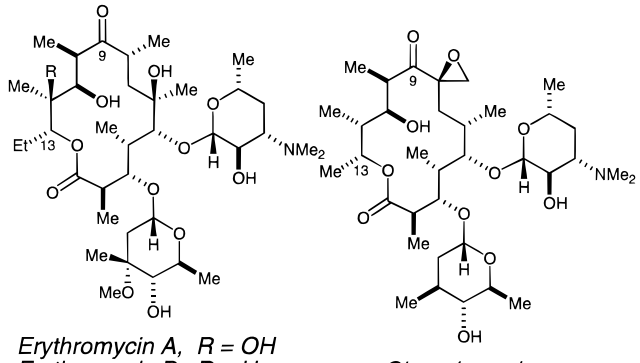
Abstract: The asymmetric syntheses of 6-deoxyerythronolide B (**1**) and oleandolide (**2**) have been achieved, each in 18 linear steps. These syntheses demonstrate the utility of chiral β-keto imide building block **3** as a versatile building block for the aldol-based assemblage of polypropionate-derived natural products.

Introduction

Since their isolation in the 1950s,[1] the erythromycins and oleandomycin have served as pivotal members of the macrolide family of antibiotics,[2] both to the practicing clinician and to the synthetic organic chemist. To the medical community, these compounds represent a mainstay of the antibacterial arsenal due to their low toxicity and high potency against Gram-positive bacteria and mycoplasma.[3] To the chemical community, these structures have stimulated the development of new reactions and concepts for acyclic stereocontrol.[4] The biological precursors of these antibiotics, 6-deoxyerythronolide B (**1**) and oleandolide (**2**), are structurally homologous, differing only in the degree of oxygenation at C_8 and of substitution at C_{14}. Indeed, each seco acid bears evidence of the individual propionate or acetate subunits that are iteratively incorporated into their respective structures during biosynthesis (Scheme 1).

A long-term objective of this research program has been to develop practical laboratory emulations of the series of acylation/reduction reactions performed by the polyketide synthases[5] and more convergent variants thereof. Highlights of this program have included the development of β-keto imides as dipropionate building blocks,[6] their diastereoselective aldol bond constructions,[7] and associated β-hydroxy ketone reductions.[8] Applications of these reactions to the synthesis of several natural product targets have recently appeared.[9] In the present investigation, we describe the syntheses of the 6-deoxyerythronolide B (**1**) and oleandolide (**2**) using this integrated reaction methodology.

Inspection of the 6-deoxyerythronolide B and oleandolide seco acids suggested plausible routes to the syntheses of the C_1-C_5 and C_9-C_{13} subunits of each from a common building block, β-keto imide **3**, through its associated aldol constructions (Scheme 2). For example, the C_1-C_5 region of each target could be established from our previously reported Ti(IV)-mediated syn aldol reactions of **3** with subsequent syn reduction of the resulting aldol adducts. Similarly, the C_9-C_{13} subunits might result from the "other" syn aldol construction, obtainable via the use of Sn(II) enolates, with subsequent application of our hydroxyl-directed anti reduction methodology. The development of β-keto imide **3** as the central building block for macrolide synthesis is demonstrated in the syntheses of the 6-deoxyerythronolide B and oleandolide described in the following sections.



Synthesis of 6-Deoxyerythronolide B

Synthesis Plan. The 6-deoxyerythronolide B synthesis plan was predicated upon the macrolactonizaton of a suitably

(1) (a) Erythromycin: McGuire, J. M.; Bunch, R. L.; Anderson, R. C.; Boaz, H. E.; Flynn, E. H.; Powell, H. M.; Smith, J. W. *Antibiot. Chemother.* **1952**, *2*, 281−283. (b) Oleandomycin: Sobin, B. A.; English, A. R.; Celmer, W. D. *Antibiot. Annu.* **1955**, 827−830.

(2) *Macrolide Antibiotics. Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: Orlando FL, 1984.

(3) Nakayama, I. In *Macrolide Antibiotics. Chemistry, Biology, and Practice*; Omura, S., Ed.; Academic Press: Orlando, FL, 1984; pp 261−298.

(4) For a review of synthetic efforts in this field dating through 1985, see: Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569−3624.

(5) (a) Cortes, J.; Haydock, S. F.; Roberts, G. A.; Bevitt, D. J.; Leadlay, P. F. *Nature* **1990**, *348*, 176−178. (b) Donadio, S.; Staver, M. J.; McAlpine, J. B.; Swanson, S. J.; Katz, L. *Science* **1991**, *252*, 675−679. (c) Malpartida, F.; Hopwood, D. A. *Nature* **1984**, *309*, 462−464.

(6) For the synthesis of β-keto imides, see: Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154−1156.

(7) For aldol bond constructions employing β-keto imide, see: (a) Evans, D. A.; Clark, J. S.; Metternich, R.; Novack, V. J.; Sheppard, G. S. *J. A.m Chem. Soc.* **1990**, *112*, 866−868. (b) Evans, D. A.; Ng. H. P.; Clark, J. S.; Rieger, D. L. *Tetrahedron* **1992**, 2127−2142.

(8) For anti reductions, see: (a) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578. (b) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449. For syn reductions, see: (c) Oishi, T.; Nakata, T. *Acc. Chem. Res.* **1984**, *17*, 338−344.

(9) (a) Lonomycin: Evans, D. A.; Ratz, A. M.; Huff, B. E.; Sheppard, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 3448−3467. (b) Rutamycin: Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446−11459. (c) Calyculin A: Evans, D. A.; Gage, J. R.; Leighton, J. L. *J. Am. Chem. Soc.* **1992**, *114*, 9434−9453.

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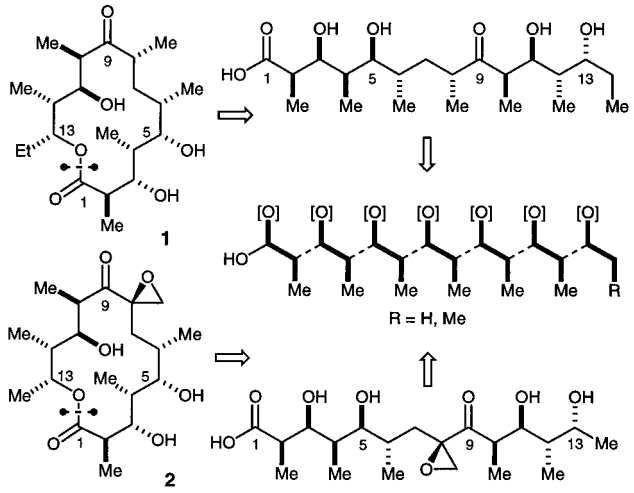
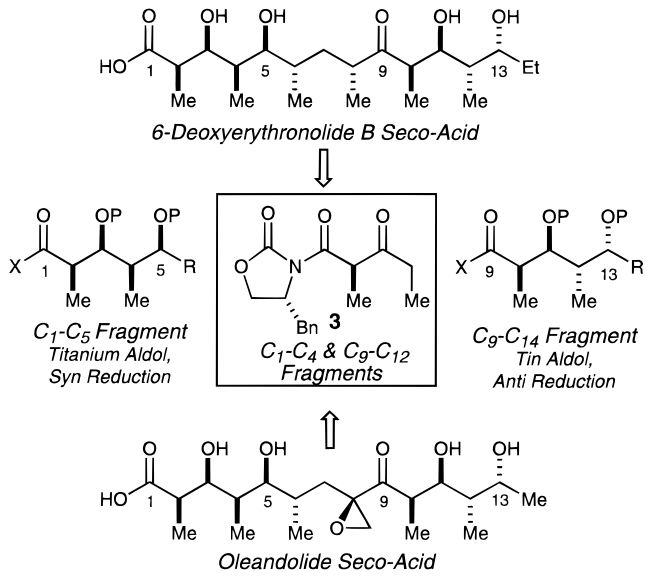
Scheme 1



protected seco acid precursor, a reaction that is now well-precedented. The resultant seco acid contains a notable degree of symmetry, particularly if the oxidation states of C_7 and C_9 are normalized to the remaining non-methyl bearing carbons as in **4** (Scheme 3). This intermediate was viewed to be an attractive target for two reasons: (1) the addition of the C_7-hydroxyl substituent extended the number of subsequent aldol disconnections that might be entertained (vide infra); (2) precedent had established that macrocyclization cannot proceed through a seco acid carrying a ketone at C_9.[10] This synthesis plan would therefore incorporate the C_7 deoxygenation event which is also present in the biosynthetic route.[5b]

Seco acid template **4**, with 12 alternating hydroxyl- and methyl-bearing stereocenters, presented several aldol coupling options. In particular, the two central aldol disconnections illustrated in Scheme 4 were attractive from the standpoint of convergency. Since the oxidation states at C_7 and C_9 were to be modified in subsequent steps in the synthesis, the only absolute stereochemical constraint in the aldol coupling process was the establishment of the requisite configuration at the C_8 methyl-bearing stereocenter. In addition, although the C_9 hydroxyl stereochemistry would ultimately be lost through oxidation, this center, as the 9-(*S*) diastereomer, has proved instrumental in obtaining good yields in the macrocyclization of other seco acid precursors containing a C_9, C_{11} cyclic protecting group.[11] Drawing upon a wealth of data on metal enolate aldol reactions,[12] the C_8-C_9 bond construction was examined first; however, an unprecedented reversal in enolate face selectivity resulted in the abandonment of this fragment coupling option[13] in favor of the successful C_7-C_8 aldol construction alternative that is developed in the ensuing discussion.

Scheme 2



Synthesis of the C_1-C_7 Subunit. β-Keto imide **3** provided convenient access to the stereochemical array contained in the C_1-C_7 substructure. Addition of methacrolein to the titanium enolate derived from β-keto imide **3** under standard conditions provided the syn aldol adduct **5** in high yield with excellent selectivity (>99:1 diastereoselection) (Scheme 4).[7b] Chelate-controlled syn reduction of the C_3-ketone with $Zn(BH_4)_2$[8c] followed by protection of the resultant diol **6** as its acetonide afforded diastereomerically pure olefin **7** in quantitative yield.[14] Hydroboration[15] of terminal olefin **7** with 9-BBN[16] proceeded with good stereoselectivity (85:15) to give a 73% isolated yield of the desired anti product diastereomer. Finally, Swern oxidation[17] completed the synthesis of this fragment in 63% overall yield.

Synthesis of the C_8-C_{15} Subunit. As with the previous fragment, the synthesis of the C_8-C_{15} substructure began with β-keto imide **3** (Scheme 5). Stannous triflate-mediated aldol reaction of β-keto imide **3** with propionaldehyde afforded a 94:6 ratio of diastereomers from which the desired adduct **10** could be crystallized in 84% yield.[7a] Quantitative reduction of aldol adduct **10** with $Na(AcO)_3BH$[8a] afforded the desired anti diol (diastereoselection >99:1)[7a] which was quantitatively monosilylated (TBSOTf) at the C_{13}-hydroxyl with complete regioselectivity. Hydroxyl-directed transamination ($AlMe_3$, Me(MeO)NH·HCl)[18] afforded Weinreb amide **12**, which upon treatment with ethylmagnesium bromide provided hydroxy ketone **13a** in good overall yield.

In anticipation of the incorporation of a C_9, C_{11} benzylidene acetal at a later point in the synthesis, the C_{11}-hydroxyl group in **13a** was masked as the *p*-methoxybenzyl (PMB) ether by treatment with benzyltrichloroacetimidate[19] and triflic acid, affording a 56% yield of the desired PMB-protected ethyl ketone

(10) Masamune, S.; Hirama, M.; Mori, S.; Ali, S. A.; Garvey, D. S. *J. Am. Chem. Soc.* **1981**, *103*, 1568−1571.

(11) (a) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Sakan, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chenevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press: J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3213−3215. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *Tetrahedron* **1990**, *46*, 4613−4628. (c) Yonemitsu, O. *J. Synth. Org. Chem., Jpn.* **1994**, *52*, 74−83.

(12) Evans, D. A.; Dart, M. J.; Duffy, J. L.; Rieger, D. L. *J. Am. Chem. Soc.* **1995**, *117*, 9073−9074 and references therein.

(13) (a) Evans D. A.; Kim A. S. *Tetrahedron Lett.* **1997**, *38*, 53−56. (b) Kim, A. S. Ph.D. Thesis, Harvard University, Dec 1996.

(14) Ng, H. P. Ph.D. Thesis, Harvard University, Aug 1993.

(15) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487−2489.

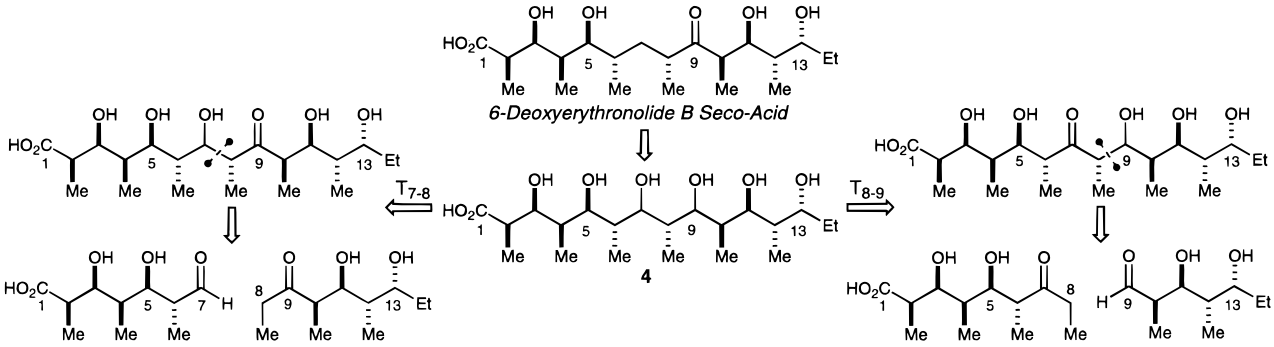
(16) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 5280−5281.

(17) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165−185.

(18) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, 4171−4174. (b) Levin, J. L.; Turos, E.; Weinreb, S. M. *Synth. Commun.* **1982**, *12*, 989−993.

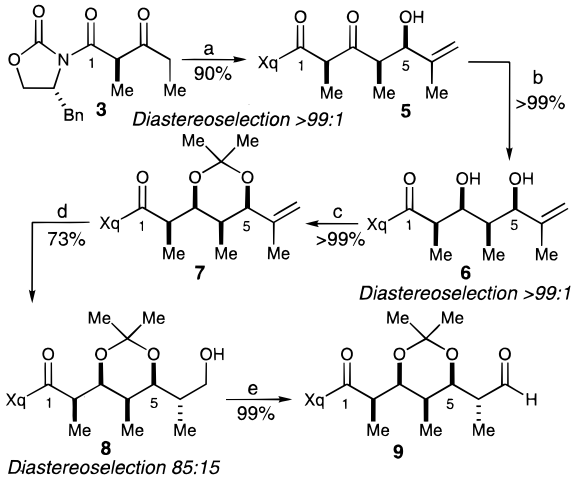
(19) Iverson, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240−1241.

Scheme 3



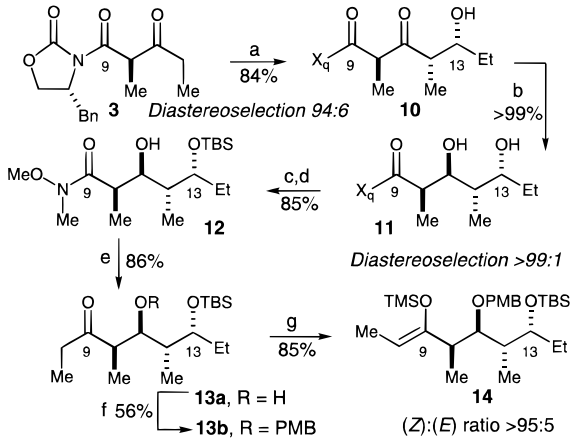
13b. Formation of the (*Z*) enolsilane **14** was achieved by selective enolization of ethyl ketone **13** with lithium bis-(dimethylphenyl)silazide,[20] and subsequent silylation of the derived lithium enolate with trimethylsilyl triflate in 85% yield. Enolization selectivity for the (*Z*) enolsilane under these conditions was >95:5.

Scheme 4



a) $TiCl_4$, *i*-Pr_2NEt, methacrolein, 0 °C, CH_2Cl_2. b) $Zn(BH_4)_2$, -78 °C, CH_2Cl_2. c) $Me_2C(OMe)_2$, CSA, RT, CH_2Cl_2. d) 9-BBN (3 equiv), THF, 0→25 °C. e) $(COCl)_2$, DMSO, Et_3N, -78 °C, CH_2Cl_2.

Scheme 5



a) $Sn(OTf)_2$, Et_3N, propionaldehyde, -78 °C, CH_2Cl_2. b) $Na(OAc)_3BH$, 25 °C, AcOH. c) TBSOTf, 2,6-lutidine, 0 °C, CH_2Cl_2. d) $AlMe_3$, (MeO)MeNH·HCl, 0 °C, CH_2Cl_2. e) EtMgBr, 0 to 25 °C, Et_2O. f) $Cl_3CC(NH)O$-(*p*-OMe)Bn, TfOH, 25 °C, CH_2Cl_2. g) *n*-BuLi, $(PhMe_2Si)_2NH$, TMSOTf, 2,6-lutidine, -78 to 25°C, THF.

Aldol Fragment Coupling. With the requisite fragments in hand, the critical aldol fragment coupling reaction was investigated. A mixture of aldehyde **9** (1.6 equiv) and enolsilane **14** (1.0 equiv) was treated with 10 equiv of $BF_3{\cdot}Et_2O$ (CH_2Cl_2, $-95 \rightarrow -78$ °C, 1.5 h) to provide the desired aldol adduct **15** in 83% yield as a single isomer (eq 1, Scheme 6). Chelate-controlled reduction of **15** with $Zn(BH_4)_2$[8c] afforded diol **16** (95% yield, >95:5 diastereoselection), thereby establishing the desired 9-(*S*) hydroxyl configuration required for macrocyclization.

Benzylidene acetal **17** was then formed as a single isomer through an anhydrous DDQ oxidation in >99% yield, differentiating the C_7 and C_9 alcohols and constraining the C_9 and C_{11} hydroxyls for macrocyclization. The significance of this stereogenic center on macrocyclization will be discussed at a later stage (vide infra). Stereochemical characterization based on coupling constants[21] and NOESY spectra of benzylidene acetal **17** and the acetonide of diol **18** (dimethoxypropane, CSA) clearly established not only the syn selectivity of the $Zn(BH_4)_2$ reduction, but also the syn selectivity for the aldol reaction (Scheme 6). Thus, all four newly formed stereocenters were established with the predicted sense of induction. Most importantly, the desired configuration of the C_8 methyl group was established with high selectivity.

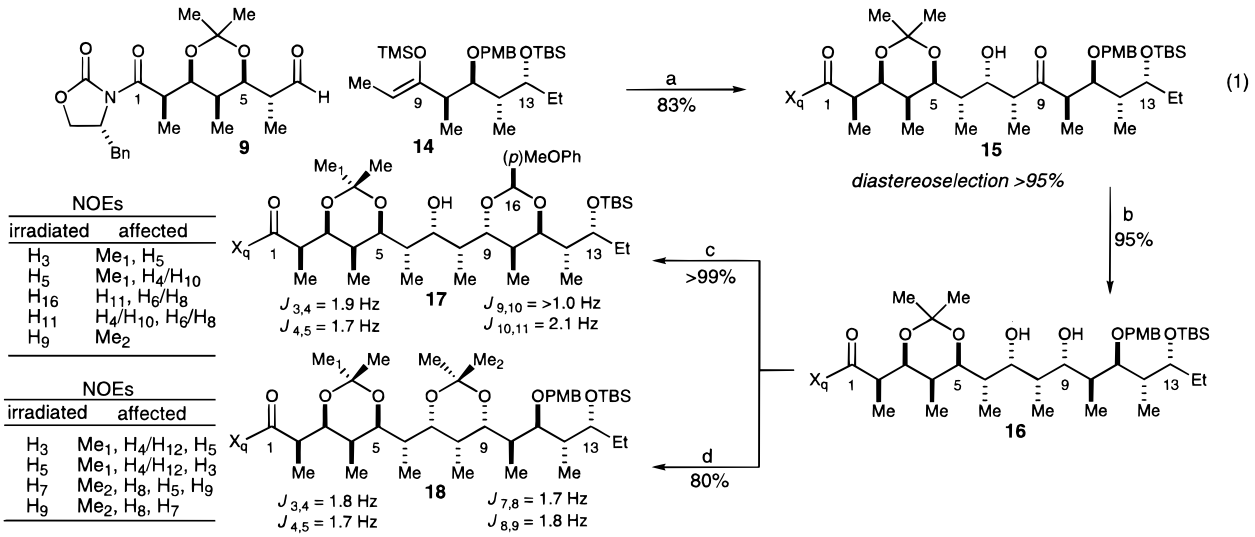
Stereochemical Analogy for the Aldol Reaction. The double stereodifferentiating C_7-C_8 aldol fragment coupling reaction described above (Scheme 6, eq 1) was designed on the basis of a series of analogous aldol processes where the impact of chirality in each of the reacting partners was individually assessed in reactions with an achiral counterpart.[22] Experiments from this independent study which are relevant to the present reaction are summarized in Scheme 7. These data establish that: (1) with chiral enolsilanes, face selectivity may be controlled by enolsilane geometry (eqs 2 and 3); (2) with chiral aldehydes, Felkin face selectivity is exceptionally high (eq 4); and (3) due to the intervention of open transition states, syn/anti diastereoselection is intrinsically low. In double stereodifferentiating Mukaiyama aldol processes, the stereochemical determinants for the forming methyl and hydroxyl stereocenters are localized in the chiral enolsilane and aldehyde reaction partners, respectively. Thus, in the double stereodifferentiating process used to assemble the erythronolide fragments (eq 1), we conclude that aldehyde **9** provides dominant control over the forming C_7-hydroxyl-bearing stereocenter while

(20) Masamune, S.; Ellingboe, J. W.; Choy, W. *J. Am. Chem. Soc.* **1982**, *104*, 5526−5528.

(21) See: (a) Evans, D. A.; Rieger, D. L.; Gage, J. R. *Tetrahedron Lett.* **1990**, *31*, 7099−7100. (b) Dart, M. J. Ph.D. Thesis, Harvard University, May 1995.

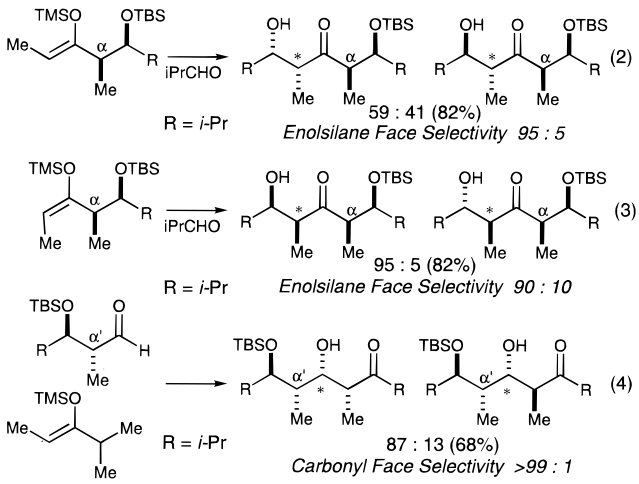
(22) Evans, D. A.; Yang, M. G.; Dart, M. J.; Duffy, J. L.; Kim, A. S. *J. Am. Chem. Soc.* **1995**, *117*, 9598−9599.

Scheme 6



enolsilane **14** dictates the stereochemistry of the forming C_8-methyl-bearing stereocenter.

Scheme 7[a]



[a]Reactions carried out with BF_3•OEt_2 (1.3 equiv), CH_2Cl_2, -78 °C for 1-2 h.

Synthesis of 6-Deoxyerythronolide B. At this juncture, all the stereocenters in the target had been installed, leaving only final refunctionalizations and macrocyclization to complete the synthesis. The C_7 position was deoxygenated in a two-step procedure through elaboration of the alcohol to the derived methyl xanthate in 84% yield (Scheme 8) and reduction via Barton radical deoxygenation.[23] This latter step required significant optimization. At a stoichiometry of 1.1 equiv of Bu_3SnH per equiv of substrate (cat. AIBN, 0.03 M in toluene, 80 °C), the desired benzylidene acetal **20** was obtained in only 20% yield (Scheme 8, Table 1). The balance of the material was obtained as a 1:1 mixture of deoxygenated *p*-methoxybenzoate regioisomers **21** and **22**. As shown in Table 1, employment of degassed solvent failed to rectify this problem and suggested a mechanism originating in intramolecular 1,5-hydrogen radical abstraction from the benzylidene acetal by the C_7 carbon radical followed by oxidative scission, possibly during isolation. Given this hypothesis, an increase in the concentration of Bu_3SnH should provide an in situ quench of the oxygen-stabilized benzyl radical. This trend was verified by a comparing the outcomes of low and high concentrations of Bu_3SnH. While at low concentration no desired product was obtained, when the reaction was carried out in neat Bu_3SnH, quantitative conversion to a 3.3:1 mixture of deoxygenated benzylidene acetals was observed (vide infra), from which the desired compound could be obtained following equilibration (CSA, CH_2Cl_2) in 84% yield.

In preparation for macrocyclization, imide hydrolysis from the carboxyl terminus and cleavage of the C_{13}-TBS protecting group was required to afford the seco acid (Scheme 9). Given the acid lability of the two cyclic protecting groups, tetrabutylammonium fluoride proved optimal for deprotection of the C_{13} alcohol. However, since β-elimination of the imide occurred at a rate competitive with deprotection, initial conversion to the carboxylic acid (LiOOH, 72% yield) was required to buffer the acidity of the α-proton. Under these conditions, desilylation was achieved in 88% yield, to afford seco acid **23**. Macrocyclization was performed as a two-step, one-flask procedure whereby an intermediate mixed anhydride was formed from 2,4,6-trichlorobenzoyl chloride[24] (1.0×10^{-2} M benzene) before treatment with excess DMAP. This procedure afforded exclusively monolide **24** (Scheme 9) in 86% yield without the use of high dilution conditions.

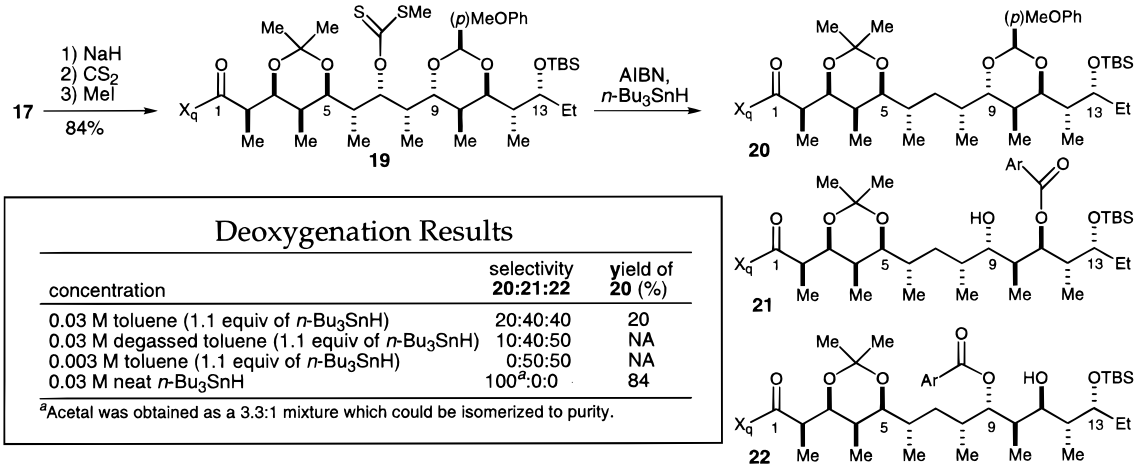
The role of the benzylidene acetal in the success of this macrocyclization merits commentary. The critical function of C_9,C_{11} cyclic protecting groups in the preorganization of the seco acid was first revealed in the Woodward erythromycin synthesis.[11] Stork has provided additional evidence for this type of conformational organization in his 9-(*S*)-dihydroerythronolide A synthesis.[25] In that investigation, only the (*R*) acetal diastereomer was successfully cyclized. Fortuitously, the single isomer obtained on our substrates, through both DDQ oxidative acetal formation and acid equilibration following the deoxygenation step, corresponded to the desired (*R*) acetal configu-

(23) (a) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574−1585. (b) Barton, D. H. R.; Dorchak, J.; Jaszberenyi, J. Cs. *Tetrahedron* **1992**, *48*, 7435−7446.

(24) See Experimental Section for more details. Also see: (a) Hikota, M.; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367−6370. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7−9. (c) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(25) Stork, G.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **1987**, *109*, 1565−1567.

Scheme 8



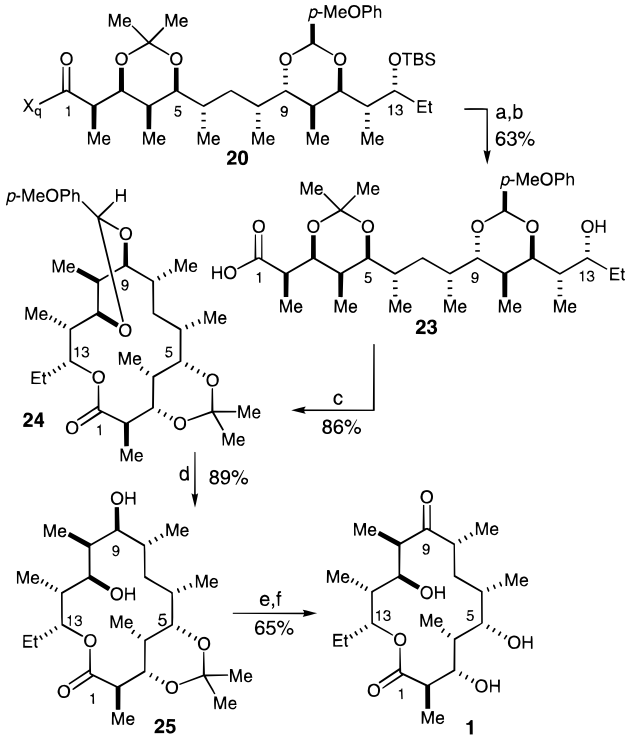
Deoxygenation Results

concentration	selectivity **20**:**21**:**22**	yield of **20** (%)
0.03 M toluene (1.1 equiv of *n*-Bu_3SnH)	20:40:40	20
0.03 M degassed toluene (1.1 equiv of *n*-Bu_3SnH)	10:40:50	NA
0.003 M toluene (1.1 equiv of *n*-Bu_3SnH)	0:50:50	NA
0.03 M neat *n*-Bu_3SnH	100[a]:0:0	84

[a]Acetal was obtained as a 3.3:1 mixture which could be isomerized to purity.

ration. Minimization of *syn*-pentane interactions within the dioxolane structure leads to the remarkable selectivity found for this acetal isomer which contains the greater number of axial substituents. Unavoidable nonbonded interactions would exist in the unobserved (*S*) acetal isomer (Scheme 10).[26] Thus, our system proved ideally geared for macrocyclization.

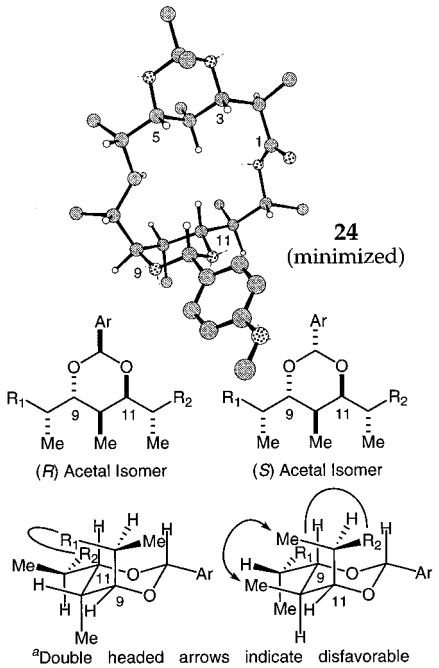
Scheme 9



a) LiOOH, 0 °C, THF. b) TBAF, 65 °C, THF. c) $Cl_3C_6H_2COCl$, *i*-Pr_2 NEt, DMAP, 25 °C, benzene. d) 20% $Pd(OH)_2$/C, 25 °C, *i*-PrOH. e) PCC, 25 °C, CH_2Cl_2. f) 1M HCl, 25 °C, THF.

Macrolactone **24** was submitted to hydrogenolysis with Pearlman's catalyst (20% $Pd(OH)_2$/C) in 2-propanol to deprotect diol **25** in 89% yield (Scheme 11).[27] PCC next effected regioselective oxidation of the C_9 carbinol[28] in 76% yield prior to acetonide deprotection under HCl/THF conditions[29] to afford the 6-deoxyerythronolide B in 85% yield. This synthetic material proved identical in all respects (^{1}H NMR, ^{13}C NMR, IR, R_f, [α]D, FAB MS) with a natural sample.

Scheme 10[a]



[a]Double headed arrows indicate disfavorable nonbonding interactions. Curved lines indicate the location of the remainder of the carbon framework which would result from macrocyclization.

Synthesis of Oleandolide

Synthesis Plan. The synthesis plan for the oleandolide (**2**) subunits[30] was closely related to the plan implemented for 6-deoxyerythronolide B (**1**) (cf. Scheme 2) where routes to the construction of the C_1-C_8 and C_9-C_{14} fragments again depended heavily on the β-keto imide methodology introduced in the preceding section. The two routes differed in the strategies that were employed at the fragment coupling stage of the syntheses. In the present synthesis, the decision was made

(26) For a related example of 1,3-anti dioxolane diastereoselectivity, see: Schreiber, S. L.; Wang, Z. *Tetrahedron Lett.* **1988**, *29*, 4085−4088.

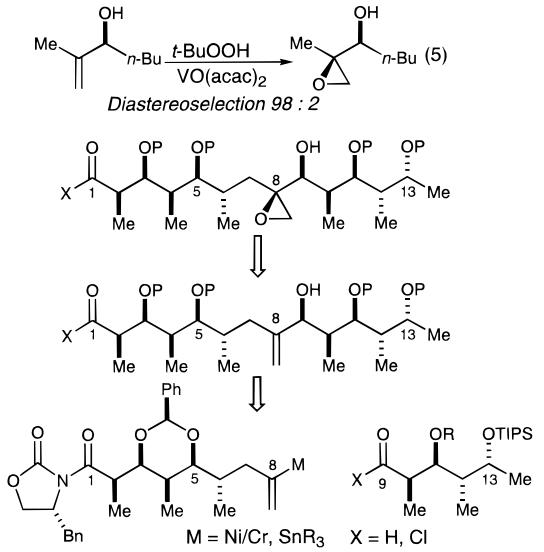
(27) This compound was synthesized previously. See: Myles, D. C.; Danishefsky, S. J.; Schulte, G. *J. Org. Chem.* **1990**, *55*, 1636−1648.

(28) (a) Corey, E. J.; Melvin, L. S. *Tetrahedron Lett.* **1975**, 929−932. (b) This same oxidation was performed by Danishefsky et al. (See ref 27).

(29) Corey, E. J.; Kim, S.; Yoo, S.; Nicolaou, K. C.; Melvin, L. S.; Brunelle, D. J.; Falck, J. R.; Trybulski, E. J.; Lett, R.; Sheldrake, P. W. *J. Am. Chem. Soc.* **1978**, *100*, 4620−4622.

(30) Evans, D. A.; Kim, A. S. *J. Am. Chem. Soc.* **1996**, *118*, 11323−11324.

Scheme 11



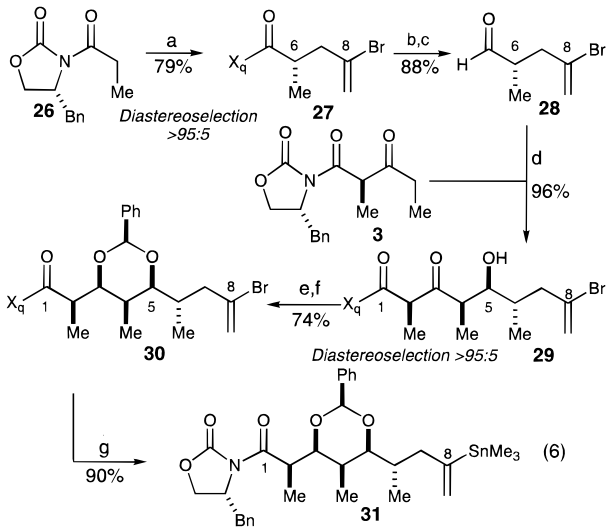
to introduce the C_8-epoxide moiety into the assembled acyclic precursor, thereby establishing all stereocenters of the molecule prior to macrocyclization (Scheme 11). In previous syntheses of oleandolide, epoxidation after macrocycle construction proved problematic since the conformation of the ring system exposes the undesired face of the 1,1-disubstituted olefin to reagent attack.[31] Although Tatsuta et al. effected stereoselective epoxidation on a macrocyclic derivative,[31] Paterson et al. were unable to duplicate this transformation on related analogues. However, in this latter synthesis, it was demonstrated that the macrocyclic epoxide could be constructed via dimethylsulfonium methylide addition to the corresponding C_8 ketone.[32]

Ample precedent exists for the directing influence of allylic alcohols in the (V^{5+})-mediated epoxidation process (eq 5).[33] Furthermore, the 9-(*S*)-hydroxyl configuration which should direct epoxidation to the desired face of the olefin would also reinforce the macrocyclization process (vide supra). The implementation of this plan is detailed in the following discussion.

Synthesis of the C_1-C_8 Subunit. The synthesis of the C_1−C_8 substructure (Scheme 12) began with the alkylation of the lithium enolate derived from imide **26** with 2,3-dibromopropene to afford product **27** in 79% yield as a single isomer, thereby establishing the C_6 stereocenter with essentially complete stereochemical control. $LiBH_4$ reduction of the imide afforded the known chiral alcohol which was subjected to subsequent Swern oxidation to provide aldehyde **28** in 88% yield over the two steps.[34]

The double stereodifferentiating aldol reaction of the titanium enolate derived from *β*-keto imide **3** with aldehyde **28** proved

Scheme 12



a) *n*-BuLi, $(i\text{-Pr})_2NH$, 2,3-dibromopropene, -78 to -35 °C. b) $LiBH_4$, 25 °C. c) $(COCl)_2$, DMSO, Et_3N, -78 °C. d) $Ti(i\text{-PrO})Cl_3$, Et_3N, **28**, -78 °C. e) $Zn(BH_4)_2$, -78 to -58 °C. f) $(MeO)_2CHPh$, CSA, 25 °C. g) $(Me_3Sn)_2$, $Pd(PPh_3)_4$, $(i\text{-Pr})_2NEt$, 80 °C, C_6H_6.

capricious. Under the normal enolization conditions ($TiCl_4$, Et_3N), a 53% yield of the desired aldol adduct **29** was obtained; however, it was found that a slightly modified titanium enolate of undefined structure ($i\text{-PrOTiCl}_3$, Et_3N) afforded significantly improved yields (95% yield, diastereoselection >95:5).[35,36] Aldol adduct **29** was then subjected to chelate-controlled reduction with $Zn(BH_4)_2$[8c] to afford the syn diol isomer (89% yield) as the only stereoisomer observed by ^1H NMR spectroscopy. The resultant C_3,C_5 diol was protected as the cyclic benzylidene acetal in 83% yield.

With the protected vinyl bromide **30** in hand, a number of vinylmetal-based carbonyl additions were explored. The Ni/Cr-mediated additions of vinyl iodides to aldehydes[37] seemed initially appealing since the desired C_9 hydroxyl stereochemistry might be established through Felkin control emanating from the C_{10} stereocenter. However, when this transformation was attempted using an appropriately configured chiral aldehyde, the undesired 9-(*R*) isomer was preferentially obtained.[13b] Vinyl bromide **30** was next converted to the corresponding vinylstannane with the intention of evaluating the Stille Pd-catalyzed acylation process.[38] Preliminary stannylation studies employed vinyl bromide **27** (Scheme 12) as a surrogate for the real system. Stannylation under various Pd-catalyzed conditions was plagued by product protodestannylation, homodimerization, and butyl transfer from the reagent bis(tributyltin). Variation of solvent, Pd source, ligand, and additional addends[39] failed to provide greater than 60% yield of the desired product. Working under

(31) (a) Paterson, I.; Norcross, R. D.; Ward, R. A.; Romea, P.; Lister, M. A. *J. Am. Chem. Soc.* **1994**, *116*, 11287−11314. (b) Tatsuta, K.; Ishiyama, T.; Tajima, S.; Koguchi, Y.; Gunji, H. *Tetrahedron Lett.* **1990**, *31*, 709−712.

(32) This procedure exploited the inherent macrocyclic conformation in establishing the correct stereochemistry, as corroborated by a detailed molecular modeling study. (See ref 31a).

(33) (a) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63−73. (b) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *49*, 4733−4736. (c) For a general review of directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.

(34) This three-step sequence was performed in the synthesis of X-206 from these laboratories with the exception that norephedrine-derived oxazolidinone was used as the chiral auxiliary. See: Evans, D. A.; Bender, S. L.; Morris, J. *J. Am. Chem. Soc.* **1988**, *110*, 2506−2526.

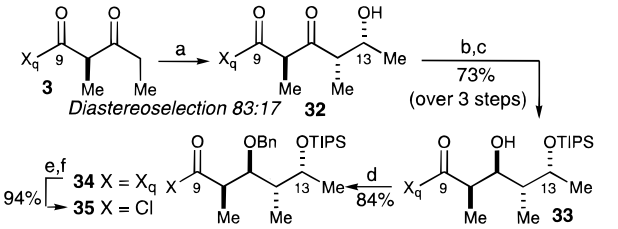
(35) In the preliminary work on Ti-mediated auxiliary-controlled aldol reactions, $Ti(i\text{-PrO})Cl_3$ was shown to exhibit slightly diminished selectivity relative to $TiCl_4$: (a) Bilodeau, M. T. Ph.D. Thesis, Harvard University, 1993. This trend is also true for Ti-mediated Michael reaction. See: (b) Evans, D. A.; Bilodeau, M. T.; Somers, T. C.; Clardy, J.; Cherry, D.; Kato, Y. *J. Org. Chem.* **1991**, *56*, 5750−5752.

(36) Use of $Ti(Oi\text{-Pr})Cl_3$ provided a more nucleophilic enolate to enhance conversion. Previous cases of diminished reactivity requiring the use of this stronger nucleophile all contained the element of α,*β*-unsaturation on the aldehyde. See refs 13b and 14.

(37) (a) Kishi, Y. *Pure and Appl. Chem.* **1992**, *64*, 343−350. (b) Chiral ligands were employed to no avail in an attempt to turn over the stereochemical induction in this reaction. See: Chen, C.; Tagami, K.; Kishi, Y. *J. Org. Chem.* **1995**, *60*, 5386-5387.

(38) (a) Labadie, J. W.; Stille, J. K. *J. Am. Chem. Soc.* **1983**, *105*, 6129−6137. (b) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634−4642.

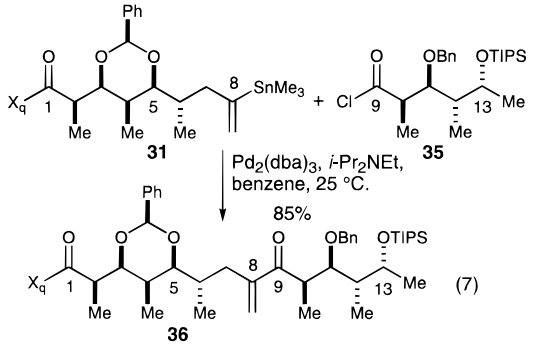
Scheme 13



the assumption that transmetalation is the rate-determining step in the catalytic cycle,[40] the addition of either weaker σ-donor ligands, such as $AsPh_3$, or of transmetalation facilitators, such as $CdCl_2$ and CuI,[37] was explored, but these modifications failed to ameliorate the problem. However, replacement of bis(tributylstannane) with the less hindered hexamethylditin[41] resulted in clean transmetalation under $Pd(PPh_3)_4$-catalyzed conditions, affording the model vinylstannane in quantitative yield. When applied to the fully elaborated system, vinylstannane **31** was formed in 90% yield (eq 6).

Synthesis of the C_9-C_{14} Subunit. As in the 6-deoxyerythronolide B synthesis, construction of the C_9-C_{14} oleandolide subunit began with a Sn(II)-mediated β-keto imide aldol reaction (Scheme 13). Addition of acetaldehyde to the Sn(II) enolate derived from **3** afforded the anticipated aldol adduct **32** under standard reaction conditions[7a] with 83:17 stereoselectivity. This result is consistent with previously established trends for this reaction which exhibited slightly diminished selectivity with smaller aldehydes.[7a] The product was most conveniently carried on without purification through quantitative $Na(AcO)_3BH$ reduction[8a] and immediate monosilylation to afford the C_5-triisopropylsilyl (TIPS) ether **33** as the sole regioisomer in 73% yield for the three-step sequence.[42] Protection of the C_{11} hydroxyl as the derived benzyl ether (benzyltrichloroacetimidate, cat. TfOH, CH_2Cl_2) proceeded in 84% yield. Orthogonally protected imide **34** was then cleaved to the carboxylic acid with LiOOH[43] at 0 °C (94% yield) prior to transformation to acid chloride **35** under Vilsmeier conditions.[44]

Stille Fragment Coupling. The Pd-catalyzed coupling between vinylstannane **31** and isobutyryl chloride was examined first to determine the precise conditions for this transformation. The optimal procedure developed for this reaction entailed treatment with $Pd_2(dba)_3$ and Hünig's base in benzene[44] at 80 °C, to suppress protodestannylation, dimerization, and olefin isomerization.[45] Under conditions similar to those established for the model system, the coupling of the actual intermediates, vinylstannane **31** and acid chloride **35**, formed the desired enone **36** at ambient temperature in 85% yield (eq 7).



Synthesis of the 9-(*R*) Macrocycle Diastereomer. The crucial reduction of the enone was undertaken to establish the 9-(*S*) hydroxyl configuration necessary to direct epoxidation at the C_8-olefin (vide supra). Although $Zn(BH_4)_2$ has been shown to chelate to β-alkoxy groups and effect stereoselective reduction of the neighboring ketone,[46] the reaction proceeded sluggishly even at ambient temperature to afford a 3:1 ratio of diastereomers, the major product obtained in only 36% yield (Scheme 14). Contrary to ample precedent for the operation of chelation control on similar substrates,[47] the major diastereomer was later identified as the undesired 9-(*R*) alcohol **37** (vide infra). Attempts to determine the relative stereochemistry of the nascent hydroxyl through its relationship with C_{11} proved futile due to the difficulty of selectively cleaving the C_{11}-benzyl ether in the presence of the other functionality. Furthermore, attempts at a Sharpless kinetic resolution epoxidation yielded no more than a trace amount of product.[48] Instead, allylic alcohol **37** was converted to carboxylic acid **38** to afford a macrocyclization precursor.[13b]

Under modified Yamaguchi conditions,[49] carboxylic acid **38** was cyclized to a 2.5:1 ratio of monolide **39** to diolide at high dilution (Scheme 14). However, sufficient monolide was obtained to ascertain that the undesired 9-(*R*) reduction isomer had predominated. A NOESY experiment performed on the monolide revealed a telltale NOE between H_9 and H_{10} supporting the stereochemical assignment of the 9-(*R*) hydroxyl configuration. Direction of the epoxidation to the undesired face of the olefin was ascertained by the presence of convincing NOE evidence, in particular the interaction between H_{11a} and H_{8b}. Attempts to invert the 9-(*R*) stereocenter of **37** under Mitsunobu conditions[50] or reduce the C_9 ketone of **36** with chiral agents[51] was thwarted by steric hindrance. Given these results, the decision was made to reconfigure the C_9-C_{14} fragment such that the C_{11}-hydroxyl moiety could be selectively revealed prior to C_9 ketone reduction. This decision was based on the

(39) (a) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org, Chem.* **1994**, *59*, 5905−5911. (b) Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585−9595.

(40) For a review on palladium-catalyzed organostannane cross-coupling reactions, see: (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. For more detailed mechanistic discussions, see: (b) Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933−4941. (c) Loar, M. K.; Stille, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 4174−4181. (d) Moravskiy, A.; Stille, J. K. *J. Am. Chem. Soc.* **1981**, *103*, 4182−4186. (e) Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434−442.

(41) Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033−3040.

(42) This protecting group was chosen to replace a TBS ether which was used in an earlier route and found to be too labile both under the acidic conditions required for benzylation and under the basic conditions required for oxazolidinone removal.

(43) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141−6144.

(44) Yoshihara, M.; Eda, T.; Sakaki, K.; Maeshima, T. *Synthesis* **1980**, 746−748.

(45) For a discussion on the use of base to suppress protodestannylation, see: Black, W. C. Ph.D. Thesis, Harvard University, Aug 1992. Trisubstituted olefins are known to isomerize under the reaction conditions to the more thermodynamically favored regioisomer (see ref 44a).

(46) Evans, D. A.; Ng, H. P.; Rieger, D. L. *J. Am. Chem. Soc.* **1993**, *115*, 11446−11459.

(47) (a) Reetz, M. T. *Acc. Chem. Res.* **1993**, *26*, 462−468 and references therein.

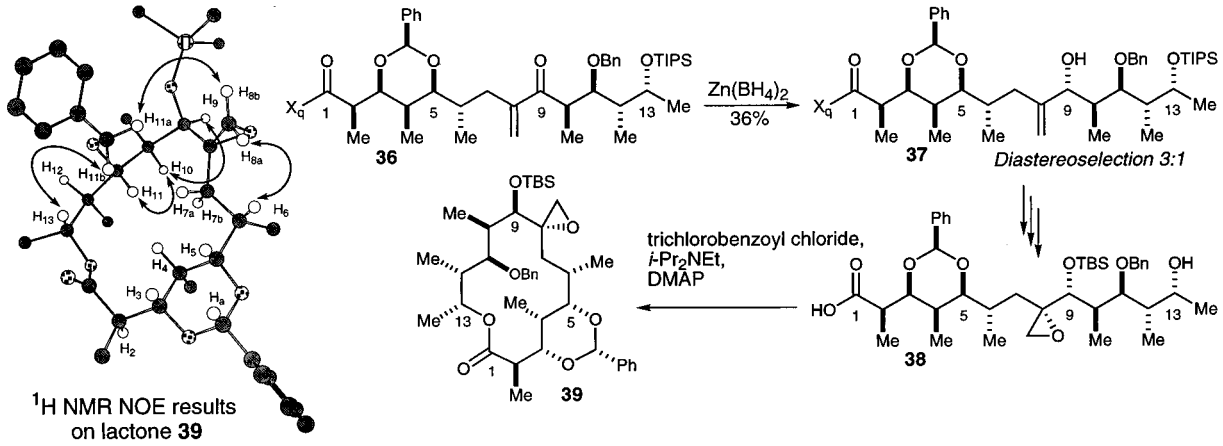
(48) (a) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc*, **1981**, *103*, 6237−6240. (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.

(49) See Experimental Section for more details. Also see ref 26.

(50) (a) Hughes, D. L.; Reamer, R. A.; Bergan, J. J.; Grabowski, E. J. J. *J. Am. Chem. Soc.* **1988**, *110*, 6487−6491. (b) Farina, V. *Tetrahedron Lett.* **1989**, *30*, 6645−6648.

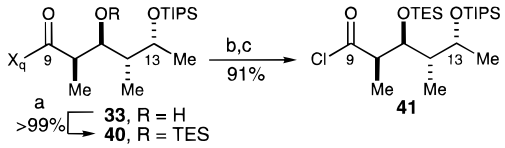
(51) Corey, E. J. *Pure Appl. Chem* **1990**, *62*, 1209−1216.

Scheme 14



assumption that an exposed hydroxyl would be more prone to participate in chelate-controlled reduction than the analogous benzyl ether.

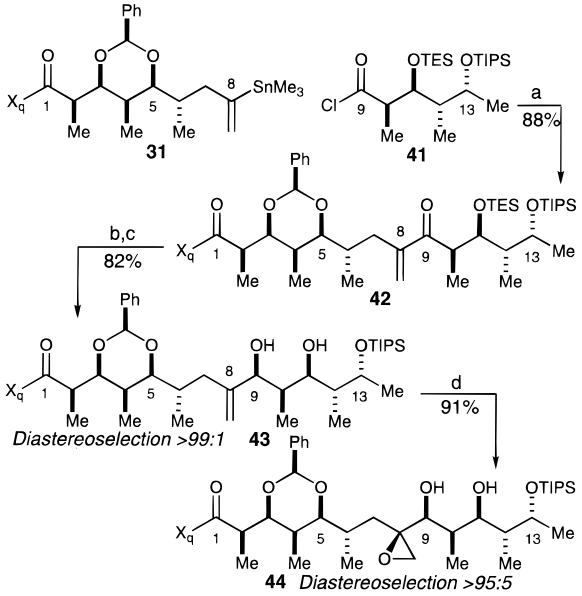
Scheme 15



a) TESOTf, 2,6-lutidine, 25 °C. b) LiOOH, 0 °C. c) $(COCl)_2$, DMF, 25 °C.

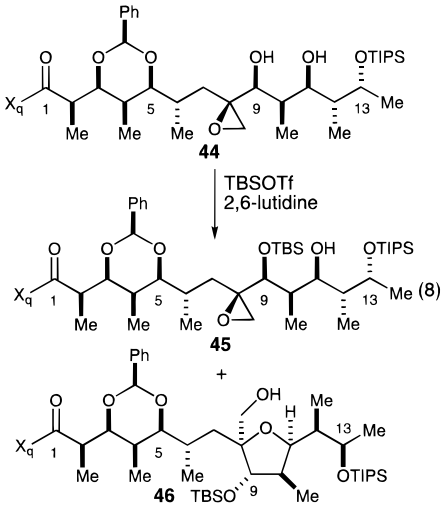
Synthesis of the 9-(*S*) Macrocycle Isomer. In the revised synthesis of the C_9-C_{14} fragment, alcohol **33** was protected with triethylsilyl triflate (TESOTf) in quantitative yield prior to hydrolysis by LiOOH in 91% yield (Scheme 15). Treatment with oxalyl chloride and DMF then afforded the acid chloride for Stille coupling with **41** without measurable loss of the labile silyl groups. Under conditions optimized for the previous route, vinylstannane **31** and acid chloride **41** were coupled in 88% yield (Scheme 16). Treatment of enone **42** with HF·pyridine at 0 °C for no more than 2.5 h then afforded 95% of the monodesilylated product without appreciable loss of the C_{13}-TIPS ether. Fortunately, chelate-controlled reduction of this substrate with $Zn(BH_4)_2$ did afford the desired diol **43** in a >99:1 ratio of diastereomers as determined by HPLC analysis of the unpurified reaction mixture. With the requisite C_9 stereoisomer in hand, we were gratified to obtain a 91% yield of a single epoxide isomer **44** from reaction with $VO(acac)_2$ and *tert*-butyl hydroperoxide. Thus, all stereocenters of oleandolide were established on an acyclic precursor in 11 linear steps from propionyl oxazolidinone.

Scheme 16



a) $Pd_2(dba)_3$, *i*Pr_2NEt, 25 °C. b) HF-pyr-pyr, 0 °C. c) $Zn(BH_4)_2$, -45 °C. d) $VO(acac)_2$, *t*-BuOOH, 25 °C.

Experience from the preceding route revealed an inherent instability of the 1,2-epoxy alcohol array toward macrocyclization conditions.[13b] As diol epoxide **44** also proved to be extremely labile,[52] its persilylation was attempted using TBSOTf (2,6-lutidine, rt) (eq 8); however, the major product isolated

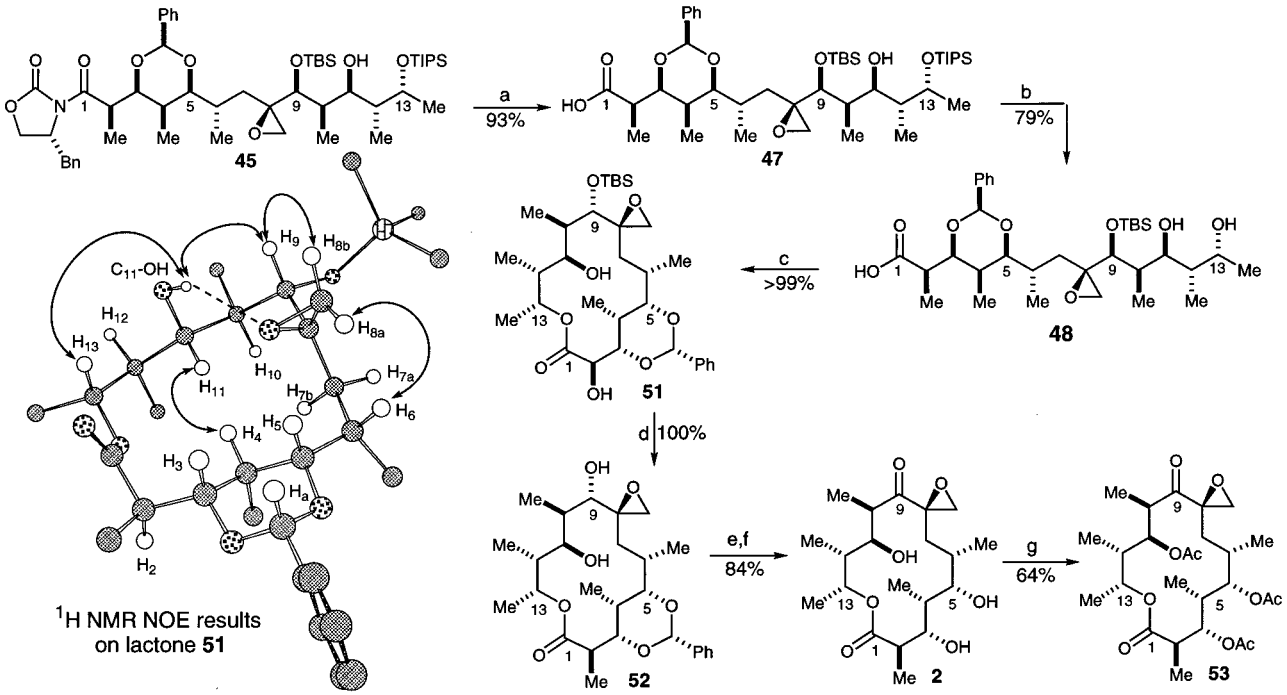


from this reaction was identified as tetrahydrofuran **46** (vide infra). Despite this demonstrated tendency toward internal ring closure, C_9-monosilylation could be achieved in 83% yield without the accompanying ring closure when silylation was carried out at low temperatures (excess TBSOTf, −78 °C). Nevertheless, C_9,C_{11}-bis(silylation) could not be achieved without concomitant rearrangement. Although epoxy alcohol **45** exhibited some acid sensitivity,[53] monoprotection sufficiently attenuated the reactivity of this intermediate so that it could be effectively carried forward in the synthesis.

(52) Diol **33** could only be purified using Et_3N-buffered silica gel.

(53) Et_3N-buffered chromatography found prophylactic use, but was not always necessary in this series of compounds.

Scheme 17



a) LiO_2H, 0 °C. b) Et_3N•HF, 25 °C, 9d. c) 2,4,6-trichlorobenzoyl chloride, *i*-Pr_2NEt, DMAP, 25 °C. d) HF•pyr, 25 °C. e) SO_3•pyr, Et_3N, 25 °C. f) 20% $Pd(OH)_2/C$, H_2, dioxane 25 °C. g) Ac_2O, DMAP, pyridine, 25 °C.

The terminal stage of the synthesis is summarized in Scheme 17. Imide hydrolysis with basic hydrogen peroxide afforded the derived carboxylic acid **47** which was isolated as the Et_3NH^+ salt in 93% yield.[54] This salt was subjected to a range of deprotection conditions designed to liberate the C_{13}-alcohol in preparation for macrocyclization while minimizing the formation of byproducts arising from tetrahydrofuran ring closure (eq 8). Under optimized conditions, Et_3N·HF provided the desired product **48** in 79% yield with minimal rearrangement to either of the tetrahydrofuran byproducts. Macrocyclization of the 9-(*S*) TBS ether **48** proceeded using modified Yamaguchi conditions[26] to afford a quantitative yield of the monolide **51**. This result is in marked contrast to the macrocyclization of the 9-(*R*) isomer (Scheme 14), where even at high dilution roughly 30% diolide was formed. It seems reasonable to attribute these empirical cyclization results to the more favorable formation of monolide from the 9-(*S*) TBS ether configuration than from the 9-(*R*) configuration which positions the sterically demanding TBS protecting group in a pseudoaxial position.[55]

The stereochemistry of all the centers in lactone **51** was confirmed by ^{1}H NMR coupling constants and a NOESY experiment. Correlation between the calculated and empirical coupling constants confirmed the correct configuration of all stereocenters on the backbone of the lactone. The stereochemistry of the hitherto unproven quaternary epoxide was suggested by the absence of NOEs between either H_{8a} or H_{8b} and the C_{11}−OH. Moreover, the regioselectivity of the C_9-silylation reaction was confirmed by the presence of the $H_9 \leftrightarrow C_{11}$−OH interaction in conjunction with an NOE between C_{11}−OH and H_{13}. Calculations also found a hydrogen bond between the C_{11}−OH and the epoxide oxygen. This interaction might have aided conversion to the macrocycle through preorganization of the seco acid.

The synthesis was completed by the removal of the C_9-TBS ether by HF·pyr at room temperature over the course of 3 days (Scheme 17). Selective oxidation of the C_9-alcohol in diol **52** was achieved using the Parikh−Doering procedure[56] (SO_3·pyridine) to afford the protected oleandolide structure in 84% yield.[10,28a] The benzylidene acetal was then hydrogenolyzed in quantitative yield (20% $Pd(OH)_2/C$, 1,4-dioxane) to afford oleandolide (**2**) as the expected 3:1 mixture of 5,9-hemiacetal and 9-keto ring-chain tautomers. The spectral and chromatographic data generated for this mixture was identical to the published data and that obtained from a natural sample. In further confirmation of the success of the synthesis, the triacetate derivative **53** was prepared and its properties also demonstrated to be identical (^{1}H NMR, ^{13}C NMR, IR, R_f, $[\alpha]_D$, FAB MS) to the published data and naturally derived material.

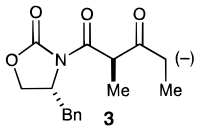
Conclusions

The syntheses of 6-deoxyerythronolide B and oleandolide were both completed in 18 linear steps from the common β-keto imide dipropionyl building block **3**. More recently, Paterson has introduced the related dipropionyl synthon (*S*)-**54** whose utility has been demonstrated in the construction of polypropionate natural products including a recent synthesis of oleandolide.[31] These two building blocks afford complementary solutions to the aldol-based assemblage of polypropionate-derived carbon chains displaying alternating methyl and hydroxyl functionality.

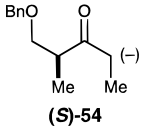
(54) Isolation of the acid as the Et_3NH^+ salt was thought to prevent not only tetrahydrofuran formation, but, on the basis of related work on 6-deoxyerythronolide B, also to inhibit α,β-elimination of the acid during silyl deprotection.

(55) Monte Carlo MM2 calculations performed for the erythronolide series revealed a distinct trend in A values for substituents at the C9 position (where 9-(*S*) is considered axial and 9-(*R*) equatorial in IUPAC nomenclature which reverses the priorities found in the erythronolide series due to the presence of the epoxide). The following values were obtained: OH, 0.88 kcal/mol; OAc, 1.27 kcal/mol; OTMS, 1.55 kcal/mol. This is consistent with the preferential closure of seco acids containing a large substituent which ultimately can achieve the pseudoequatorial position on the macrocycle. Similar calculations were performed by Paterson. See ref 31a.

(56) Parikh, J. R.; von E. Doering, W. *J. Am. Chem. Soc.* **1967**, *89*, 5505−5507.



3



(*S*)-54

Our goals in undertaking these syntheses have been twofold: (1) we have demonstrated the application of our chiral aldol methodology in the construction of propionate fragments; and (2) we identified convergent fragment coupling strategies which address the installation of remaining functionalization and cyclization of this family of macrolide antibiotics. The syntheses of 6-deoxyerythronolide B and oleandolide clearly demonstrate the rapid assembly of the chiral subunits using the β-keto imide dipropionyl building block **3** which required minimal refunctionalization to ready the fragments for coupling. This flexibility facilitated the exploration of several different coupling strategies en route to the targets. From this brief survey, it is possible, in retrospect, to envision that 6-deoxyerythronolide B as well as several other members of this family also might be convergently constructed using the Stille coupling strategy followed either hydrogenation or oxygenation.

Experimental Section[57]

(4*R*)-4-Benzyl-3-[(2*R*,4*R*,5*R*)-5-hydroxy-2,4,6-trimethyl-1,3-dioxo-6-hepteyl]-2-oxazolidinone (5). To solution of 5.70 g (19.7 mmol) β-keto imide in 80 mL of CH_2Cl_2 at −5 °C was add via syringe 2.38 mL (21.7 mmol) of $TiCl_4$ neat, affording a dark yellow solution which was treated immediately with 3.89 mL (21.7 mmol) of Hünig's base. The resultant deep red solution was stirred 1 h at −5 °C, before it was cooled to −78 °C. Methacrolein which had been freshly distilled two times was added at this time (3.26 mL, 39.4 mmol). After stirring at −78 °C for 30 min, the reaction was warmed to −50 °C and stirred for an additional 30 min. A second equal portion of methacrolein was then added and the reaction stirred for 30 min at −50 °C. To the resultant brown solution was added 100 mL of pH 7 buffer, and the mixture was stirred vigorously as it warmed to ambient temperature. The mixture was partitioned between 100 mL of saturated aqueous NH_4Cl and 150 mL of Et_2O, and the layers separated. The aqueous layer was extracted with Et_2O (2 × 50 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 100 mL) and brine (1 × 100 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo, to afford 7.00 g (99% mass balance) of a pale yellow oil. Analysis of the unpurified reaction mixture by ^{1}H NMR spectroscopy revealed a >95:5 ratio of isomers and 90% conversion. The material was generally carried on without further purification. However, some of the major diastereomer was isolated without epimerization or lactonization by flash chromatography (20% EtOAc/hexanes). Data for the isolated diastereomer: $[\alpha]^{23}_D$ −135.1° (*c* 1.02, CH_2Cl_2); IR (solution, CH_2Cl_2) 3542, 3029, 2987, 2945, 2882, 1776, 1713, 1692, 1452 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.19 (m, 5H), 5.14 (dt, J = 1.7, 0.9 Hz, 1H), 4.97 (dt, J = 1.4, 2.9 Hz, 1H), 4.87 (q, J = 7.3 Hz, 1H), 4.76 (m, 1H), 4.62 (app s, 1H), 4.28 (app t, J = 8.1 Hz, 1H), 4.19 (dd, J = 9.1, 3.0 Hz, 1H), 3.30 (dd, J = 13.4, 3.3 Hz, 1H), 2.98 (dq, J = 7.1, 2.1 Hz, 1H), 2.88 (d, J = 3.0 Hz, 1H), 2.79 (dd, J = 13.4, 9.5 Hz, 1H), 1.72 (s, 3H), 1.49 (d, J = 7.3 Hz, 3H), 1.07 (d, J = 7.1 Hz, 3H); TLC R_f = 0.75 (5% acetone/CH_2Cl_2). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 382.1630, found 382.1635.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*S*,5*R*)-3,5-dihydroxy-2,4,6-trimethyl-1-oxo-6-hepenyl]-2-oxazolidinone (6). To a clear yellow solution of purified aldol adduct (7.07 g, 19.7 mmol) in 400 mL of CH_2Cl_2 at −78 °C was added a solution of Zn(BH$_4$)$_2$ in Et_2O (150 mL, 0.2 M solution). The resultant clear solution was stirred for 15 min at −78 °C before the reaction was quenched by the addition 300 mL of a saturated aqueous solution of NH_4Cl at −78 °C. The mixture was stirred vigorously as it was warmed to ambient temperature. After 10 min at ambient temperature, the mixture was diluted with 100 mL of CH_2Cl_2, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resultant clear colorless oil was azeotroped with MeOH (5 × 300 mL) and acetic acid (1 × 5 mL) with the first MeOH azeotrope, followed by heptane (1 × 300 mL) to obtain 7.22 g (100%) of a clear colorless foam. Analysis of the unpurified material by ^{1}H NMR spectroscopy revealed a >95:5 ratio of diastereomers. This material was carried on unpurified to the next reaction. However, some of the major diastereomer could be isolated without epimerization or lactonization by flash chromatography (30% EtOAc/hexanes). Data for the isolated diastereomer: $[\alpha]^{23}_D$ −72.2° (*c* 1.05, CH_2Cl_2); IR (solution, CH_2Cl_2) 3532, 3029, 2977, 2935, 1781, 1692, 1457 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.19 (m, 5H), 5.03 (s, 1H), 4.93 (d, J = 1.3 Hz, 1H), 4.69 (m, 1H), 4.23 (app t, J = 7.6 Hz, 1H), 4.23 (app s, 1H), 4.19 (dd, J = 9.1, 3.0 Hz, 1H), 4.10 (ddd, J = 6.2, 4.3, 2.8 Hz, 1H, C_3-*H*), 4.01 (app quint, J = 6.7 Hz, 1H, C_2-*H*), 3.25 (dd. J = 13.4, 3.3 Hz, 1H), 3.06 (d, J = 2.8 Hz, 1H), 2.78 (dd, J = 13.4, 9.5 Hz, 1H), 2.41 (d, J = 2.3 Hz, 1H), 1.80 (m, 1H), 1.69 (s, 3H), 1.34 (d, J = 6.8 Hz, 3H), 0.88 (d, J = 7.0 Hz, 3H); TLC R_f = 0.09 (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 384.1787, found 384.1788.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(4*S*,5*S*,6*R*)-6-(1-methylethenyl)-2,2,5-trimethyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (7). To a solution of 14.2 g diol (39.4 mmol) in 400 mL of 2,2-dimethoxypropane at ambient temperature was added 100 mg (0.430 mmol) of CSA. The resultant mixture was stirred at ambient temperature for 4 h before being quenched by the addition of 10.0 mL of Et_3N. After filtration through 30 mL of silica, the solution was concentrated in vacuo, and purified by flash chromatography (linear gradient 7 to 20% EtOAc/hexanes, 11 × 16 cm SiO_2) to afford 14.2 g (90% over three steps) of a white moist crystalline solid: $[\alpha]^{23}_D$ −83.7° (*c* 1.27, CH_2Cl_2); IR (neat) 3029, 2990, 2937. 2880, 1783, 1693, 1454 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.20 (m, 5H), 5.01 (s, 1H), 4.87 (ddd, J = 1.5, 1.3, 1.0 Hz, 1H), 4.68 (m, 1H), 4.30 (app s, 1H), 4.20 (app t, J = 9.2 Hz, 1H), 4.19 (dd, J = 6.8, 2.1 Hz, 1H), 4.17 (dd, J = 9.2, 2.9 Hz, 1H), 3.88 (dq, J = 6.8, 9.7 Hz, 1H), 3.22 (dd, J = 13.4, 3.4 Hz, 1H), 2.74 (dd, J = 13.3, 9.6 Hz, 1H), 1.72 (ddq, J = 7.0, 2.3, <1.0 Hz, 1H), 1.53 (s, 3H), 1.46 (s, 3H), 1.42 (s, 3H), 1.31 (d, J = 6.8 Hz, 3H), 0.66 (d, J = 7.0 Hz, 3H); TLC R_f = 0.78 (5% acetone/CH_2Cl_2). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 424.2100, found 424.2093.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(4*S*,5*R*6*S*)-6-[(1*S*)-2-hydroxy-1-methylethyl)]-2,2,5-trimethyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (8). To a solution of 1.02 g (2.55 mmol) of alcohol in 25.5 mL of THF at 0 °C was added a solution of 374 mg

(57) General information is provided in the Suppporting Information and is similar to that found in ref 9c with the following exceptions. Infrared spectra were recorded on a Perkin-Elmer model 1600 FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM-500 (500 MHz) or AM-400 (400 MHz) spectrometers. NOESY experiments were performed on a Bruker DMX-500 spectrometer. Full NMR peak assignments and 13C NMR data are available in the Suppporting Information.

(1.53 mmol) 9-BBN dimer in 2.55 mL of THF via cannula (1 mL rinse). After 4 h at 0 °C, the reaction was warmed to ambient temperature for an additional 13 h. The mixture was recooled to 0 °C and quenched by the addition of 10 mL of pH 7 buffer, 10 mL of MeOH, 10 mL of a 30% aqueous solution of H_2O_2, and 5 mL of THF. After the mixture was stirred for 1 h, a 1.5 M Na_2SO_3 aqueous solution was added, and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR spectroscopy analysis of the unpurified reaction mixture showed a 85:15 mixture of diastereomers. The major diastereomer was purified by flash chromatography (linear gradient 27 to 40% EtOAc/hexanes, 3 × 21 cm SiO_2) to yield 0.636 g (60%) of a clear colorless oil: $[\alpha]^{23}_D$ −51.8° (*c* 0.965, CH_2Cl_2); IR (solution, CH_2Cl_2) 3508, 3056, 2978, 1781, 1694, 1454 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.18 (m, 5H), 4.70 (m, 1H), 4.23 (app t, J = 9.2 Hz, 1H), 4.19 (dd, J = 9.2, 3.0 Hz, 1H), 4.15 (dd, J = 9.8, 2.1 Hz, 1H), 3.93 (dq, J = 6.8, 9.8 Hz, 1H), 3.79 (dd, J = 9.8, 1.9 Hz, 1H), 3.61 (app t, J = 8.0, 10.8, 9.1 Hz, 1H), 3.54 (ddd, J = 10.8, 3.4, 9.1 Hz, 1H), 3.23 (dd, J = 13.3, 3.4 Hz, 1H), 3.10 (d, J = 9.1 Hz, 1H), 2.75 (dd, J = 13.4, 9.6 Hz, 1H), 1.90 (m, 1H), 1.65 (m, 1H), 1.49 (s, 3H), 1.40 (s, 3H), 1.30 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 7.0 Hz, 3H), 0.75 (d, J = 7.0 Hz, 3H); TLC R_f = 0.24 (50% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 442.2206, found 442.2214.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(4*S*,5*R*6*R*)-6-[(1*R*)-2-oxo-1-methylethyl)]-2,2,5-trimethyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (9). To −78 °C solution of 0.270 mL (0.540 mmol) of a 2.0 M solution of oxalyl chloride in CH_2Cl_2 in an additional 2.5 mL of CH_2Cl_2 was added rapidly via syringe 76.6 μL (1.08 mmol) of DMSO, resulting in gas evolution. After 10 min, the resultant cloudy solution was treated with a solution of 150 mg (0.360 mmol) of alcohol in 0.5 mL of CH_2Cl_2 via cannula, followed by a 0.30 mL rinse. The white mixture was stirred at −78 ° C for 15 min before 0.314 mL (1.80 mmol) of Hünig's base was added, during which addition the solution gradually became homogeneous. After 30 min, the reaction was warmed to 0 °C and maintained at that temperature for 1 h before the addition of 3 mL of a saturated NH_4Cl aqueous solution. Following dilution with 1 mL of H_2O and 2 mL of CH_2Cl_2, the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a pale yellow oil. The residue was purified by flash chromatography (20% EtOAc/hexanes, 3 × 5 cm SiO_2), affording 0.145 g (100%) of a white foam: $[\alpha]^{23}_D$ −81.5° (*c* 0.855, CH_2Cl_2); IR (neat) 2989, 2938, 2882, 2722, 1781, 1726, 1693, 1455 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 9.59 (d, J = 2.5 Hz, 1H), 7.23−7.08 (m, 5H), 4.58 (m, 1H), 4.11 (app t, J = 9.1 Hz, 1H), 4.07 (dd, J = 8.8, 2.9 Hz, 1H), 4.06 (dd, J = 9.8, 2.0 Hz, 1H), 3.95 (dd, J = 10.2, 2.1 Hz, 1H), 3.81 (dq, J = 6.8, 9.7 Hz, 1H), 3.11 (dd, J = 13.4, 3.4 Hz, 1H), 2.63 (dd, J = 13.4, 9.6 Hz, 1H), 2.37 (ddq, J = 10.2, 2.6, 7.0 Hz, 1H), 1.53 (m, 1H), 1.32 (s, 3H), 1.25 (s, 3H), 1.19 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 7.1 Hz, 3H), 0.71 (d, J = 6.9 Hz, 3H); TLC R_f = 0.65 (50% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 440.2049, found 440.2048.

(4*R*)-4-Benzyl-3-[(2*R*,4*S*,5*R*)-5-hydroxy-2,4-dimethyl-1,3-dioxoheptyl]-2-oxazolidinone (10). To a suspension of 42.3 g (102 mmol) of stannous triflate in 400 mL of CH_2Cl_2 at ambient temperature was added 14.2 mL (102 mmol) of Et_3N. The resultant pale yellow slurry was then cooled immediately to −20 °C and stirred for 5 min before a solution of 26.0 g (90.0 mmol) of β-keto imide in 100 mL of CH_2Cl_2 was added via cannula over 10 min. The resultant nearly clear solution was stirred at −20 °C for 1 h. The reaction was then cooled to −78 °C and treated with 7.36 mL (102 mmol) of freshly distilled propionaldehyde. After stirring for 1 h at −78 °C, the reaction was rapidly added via cannula to a vigorously stirring mixture of 1.5 L of CH_2Cl_2 and 1.5 L of 1 *N* $NaHSO_4$ at 0 °C. The mixture was stirred for 30 min until both layers became clear, whereupon the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL). The combined organic extracts were washed with a saturated solution of $NaHCO_3$ (1 × 500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a clear colorless oil. The unpurified mixture was analyzed by HPLC (Zorbax 40% EtOAc/hexanes, flow rate 2.0 mL/min, 254.4 nm) to reveal a 94:6 ratio of diastereomers. Purification by recrystallization (10% EtOAc/hexanes) afforded large crystalline plates (26.23 g, 84%): $[\alpha]^{23}_D$ −96.5° (*c* 1.03, CH_2Cl_2); IR (neat) 3532, 2974, 2940, 1780, 1713, 1692, 1454 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.17 (m, 5H), 4.85 (q, J = 7.3 Hz, 1H), 4.73 (m, 1H), 4.23 (app t, J = 8.1 Hz, 1H), 4.16 (dd, J = 9.1, 2.9 Hz, 1H), 3.80 (ddd, J = 8.3, 5.0, 2.9 Hz, 1H), 3.28 (dd, J = 13.4, 3.3 Hz, 1H), 2.79 (dq, J = 7.1, 2.9 Hz, 1H), 2.75 (dd, J = 13.4, 9.6 Hz, 1H), 2.52 (s, 1H), 1.3−1.6 (m, 2H), 1.46 (d, J = 7.3 Hz, 3H), 1.22 (d, J = 7.1 Hz, 3H, 0.95 (t, J = 7.5 Hz, 3H); TLC R_f = 0.53 (50% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 370.1630, found 370.1624.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*S*,5*R*)-3,5-dihydroxy-2,4-dimethyl-1-oxoheptyl]-2-oxazolidinone (11). To 500 mL of acetic acid at 0 °C was added portionwise 12.1 g (320 mmol) of $NaBH_4$. Upon completion of gas evolution, the reaction was allowed to warm to ambient temperature where it was stirred for 1 h. To this solution was added via cannula a solution of 11.1 g (32.0 mmol) aldol adduct in 100 mL of acetic acid over the course of 20 min. After an additional 30 min, the reaction was concentrated in vacuo before it was partitioned between 500 mL of a saturated aqueous solution of $NaHCO_3$ and 500 mL of CH_2Cl_2. The aqueous layer was separated and extracted by CH_2Cl_2 (1 × 300 mL). The combined organic layers were then dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was azeotroped with MeOH (5 × 400 mL) with the addition of 5 mL of acetic acid during the first round, and with heptane (1 × 400 mL), to obtain 11.2 g (100%) of a clear colorless foam that could not be further purified without concomitant lactonization: $[\alpha]^{23}_D$ −40.3° (*c* 1.07, CH_2Cl_2); IR (neat) 3426, 3026, 2964, 2933, 1780, 1692, 1456 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.17 (m, 5H), 4.67 (m, 1H), 4.20 (app t, J = 9.1 Hz, 1H), 4.15 (dd, J = 9.1, 3.0 Hz, 1H), 3.96 (dd, J = 3.0, 8.6 Hz, 1H), 3.89 (dq, J = 3.1, 7.0 Hz, 1H), 3.75 (ddd, J = 2.3, 4.3, 8.9 Hz, 1H), 3.22 (dd, J = 13.4, 3.3 Hz, 1H), 2.78 (dd, J = 13.4, 9.3 Hz, 1H), 2.01 (s, 1H), 1.79 (m, 1H), 1.38−1.57 (m, 2H), 1.25 (d, J = 7.0 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H), 0.85 (d, J = 7.1 Hz, 3H); TLC R_f = 0.15 (50% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 372.1787, found 372.1785.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*,5*R*)-5-(*tert*-butyldimethylsiloxy)-3-hydroxy-2,4-dimethyl-1-oxoheptyl]-2-oxazolidinone (11a). To a solution of 11.2 g (32.0 mmol) of diol in 600 mL of CH_2Cl_2 at −5 °C was added 4.49 mL (38.5 mmol) of 2,6-lutidine, followed by 8.26 mL (35.3 mmol) of TBSOTf. The resultant clear colorless solution was stirred at −5 °C for 1 h before the addition of 400 mL of a saturated solution of aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted

with CH_2Cl_2 (2 × 200 mL). The combined organic extracts were washed with 1 *N* HCl (1 × 200 mL) and brine (1 × 200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (20% EtOAc/hexanes) to yield 14.8 g (100%) of a clear colorless oil: $[\alpha]^{23}_D$ −1.60° (*c* 1.00, CH_2Cl_2); IR (neat) 3465, 2957, 2859, 1782, 1703, 1461 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.17 (m, 5H), 4.69 (m, 1H), 4.22 (s, 1H), 4.21 (app t, J = 8.6 Hz, 1H), 4.15 (dd, J = 9.1, 2.5 Hz, 1H), 4.01 (dd, J = 2.0, 9.8 Hz, 1H), 3.86 (dq, J = 2.1, 6.9 Hz, 1H), 3.78 (ddd, J = 2.6, 5.9, 8.2 Hz, 1H), 3.35 (dd, J = 13.3, 3.1 Hz, 1H), 2.75 (dd, J = 13.3, 9.8 Hz, 1H), 1.83 (m, 1H), 1.55 (m, 2H), 1.22 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 7.6 Hz, 3H), 0.89 (s, 9H), 0.85 (d, J = 7.1 Hz, 3H), 0.12 (s, 3H), 0.08 (s, 3H); TLC R_f = 0.73 (5% acetone/CH_2Cl_2). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 486.2652, found 486.2646.

(2*R*,3*S*,4*R*,5*R*)-5-(*tert*-Butyldimethylsiloxy)-3-hydroxy-*N*-methoxy-*N*,2,4-trimethylheptamide (12). To a stirred suspension of 3.32 g (34.0 mmol) of Weinreb salt in 44 mL of CH_2Cl_2 at −10 °C was added dropwise 17.0 mL of a 2.0 M solution of $AlMe_3$ in toluene over the course of 5 min, during which time the mixture gradually became clear. Gas evolution was evident. The resultant solution was stirred at ambient temperature for 30 min before it was again cooled to −10 °C and a solution of 5.25 g (11.3 mmol) of alcohol in 94 mL of CH_2Cl_2 was added via cannula (10-mL rinse). The resultant solution was cooled to −14 °C and allowed to sit for 9 h before it was quenched by the addition of 130 mL of a saturated aqueous solution of Rochelle's salt. The mixture was stirred vigorously until the phases became clear. The aqueous layer was then extracted with CH_2Cl_2 (1 × 50 mL). The combined organic layers were washed with H_2O (1 × 30 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (linear gradient 15 to 20% EtOAc/hexanes) to afford 3.37 g (86%) of a clear colorless oil: $[\alpha]^{23}_D$ −1.7° (*c* 1.30, $CHCl_3$); IR (solution, $CHCl_3$) 3456, 3022, 2962, 2938, 1633, 1462 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06 (s, 1H), 4.00 (dt, J = 1.6, 7.7 Hz, 1H), 3.72 (dd, J = 8.9, <1.0 Hz, 1H), 3.67 (s, 3H), 3.16 (s, 3H), 2.99 (app q, J = 4.6 Hz, 1H), 1.60 (m, 1H), 1.48 (m, 2H), 1.12 (d, J = 7.0 Hz, 3H), 0.84 (s, 9H), 0.81 (t, J = 7.5 Hz, 3H), 0.76 (d, J = 6.9 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); TLC R_f = 0.53 (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 370.2390, found 370.2381.

(4*R*,5*S*,6*R*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-5-hydroxy-4,6-dimethyl-3-oxononane (13a). To a solution of 7.39 g (21.3 mmol) of the Weinreb amide in 213 mL of Et_2O at 0 °C was added 63.9 mL (63.9 mmol) of a 1.0 M solution of ethyl Grignard. After 3 h the solution was warmed to ambient temperature and allowed to stir for 2 additional hours. The reaction was recooled to 0 °C and quenched with 100 mL of a saturated aqueous solution of NH_4Cl with concomitant gas evolution. To this white mixture was added 100 mL of Et_2O, and the resultant mixture was warmed to ambient temperature over the course of 4 h with vigorous stirring. The aqueous layer was then separated and extracted with Et_2O (2 × 100 mL). The combined organic layers were washed with 1 *N* HCl (1 × 100 mL), saturated aqueous $NaHCO_3$ (1 × 100 mL), and brine (1 × 100 mL), then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The resultant yellow oil was purified by flash chromatography (linear gradient 5 to 10% EtOAc/hexanes, 7 × 20 cm SiO_2) to afford 611 mg (8%) recovered starting material and 5.78 g (86%) of a clear colorless oil: $[\alpha]^{23}_D$ +11.4° (*c* 1.09, CH_2Cl_2); IR (neat) 3481, 2959, 2937, 2883, 2858, 1704, 1462 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 4.01 (dt, J = <1.0, 1.8, 9.8 Hz, 1H), 3.90 (s, 1H), 3.78 (ddd, J = 2.6, 6.5, 5.7 Hz, 1H), 2.51 (m, 3H), 1.71 (m, 1H), 1.53 (m, 2H), 1.10 (d, J = 7.0 Hz, 3H), 1.05 (t, J = 7.5 Hz, 3H), 0.87 (t, J = 7.5 Hz, 3H), 0.85 (s, 9H), 0.76 (d, J = 6.9 Hz, 3H), 0.09 (s, 3H), 0.06 (s, 3H); TLC R_f = 0.75 (35% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 317.2512, found 317.2502.

(4*R*,5*S*,6*R*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-5-[(*p*-methoxybenzyl)oxy]-4,6-dimethyl-3-oxononane (13b). To a solution of 2.00 g (6.33 mmol) of alcohol in 30 mL of Et_2O at 0 °C was added 1.81 mL (9.49 mmol) of unpurified *p*-methoxybenzyl trichloroacetimidate. To the resultant yellow solution was added 5 drops of a solution of triflic acid in Et_2O (5 drops triflic acid in 5 mL of Et_2O). The reaction was allowed to warm to ambient temperature. After 2.5 h, a second allotment of acetimidate was added (1.81 mL). After 7 h, a third addition was made of equal amount, and thereafter every 2 h an addition was made, up to a total of 6 (10.9 mL, 56.9 mmol total). The reaction was quenched by the addition of 30 mL of a saturated aqueous solution of $NaHCO_3$. The aqueous layer was isolated and extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was was purified by flash chromatography (first column loaded with CH_2Cl_2, eluted with 5% EtOAc/hexanes, 5 × 24.5 cm SiO_2; second column loaded and eluted with 5% EtOAc/hexanes, 5 × 25 cm SiO_2) to afford 1.55 g (56%) of a clear colorless oil: $[\alpha]^{23}_D$ −57.2° (*c* 1.12, CH_2Cl_2); IR (neat) 2957, 2936, 2882, 2857, 1713, 1614, 1514, 1462 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 4.33 (d, J = 10.3 Hz, 1H), 4.26 (d, J = 10.3 Hz, 1H), 3.97 (dt, J = 5.3, 1.8 Hz, 1H), 3.95 (dd, J = 2.5, 9.3 Hz, 1H), 3.77 (s, 3H), 2.66 (dq, J = 7.3, 1.9 Hz, 1H), 2.63 (app quint, J = 7.3 Hz, 1H), 2.48 (m, 1H), 1.70 (m, 1H), 1.53 (m, 2H), 1.12 (d, J = 7.0 Hz, 3H), 1.07 (t, J = 7.5 Hz, 3H), 0.89 (s, 9H), 0.80 (t, J = 7.5 Hz, 3H), 0.78 (d, J = 6.9 Hz, 3H), 0.07 (s, 3H), 0.06 (s, 3H); TLC R_f = 0.67 (20% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 459.2907, found 459.2922.

(*Z*)-(4*R*,5*S*,6*R*,7*R*)-7-(*tert*-Butyldimethylsiloxy)-5-[(*p*-methoxybenzyl)oxy]-4,6-dimethyl-3-(trimethylsiloxy)-2-nonene (14). To a solution of 1.33 mL (4.60 mmol) of diphenyltetramethyldisilazine in 23 mL of THF at 0 °C was added via syringe 2.88 mL (4.60 mmol) of a 1.6 M solution of *n*-butyllithium in hexanes. After 15 min, the reaction was cooled to −78 °C and a solution of 1.82 g (4.18 mmol) of ketone in 5.0 mL of THF was added via cannula (with 2 × 2-mL rinses). The resultant clear yellow solution was stirred at −78 °C for 20 min, then at 0 °C for 30 min, before 2.42 mL (20.9 mmol) of 2,6-lutidine was added, followed by 8.23 mL (16.7 mmol) of trimethylsilyl triflate in a dropwise fashion. The resultant clear colorless solution was stirred for 1 h at 0 °C, then warmed to ambient temperature and stirred for 8 h. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were then washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated to afford a yellow oil. Analysis of the unpurified mixture revealed a >95:5 ratio of olefin isomers. Purification by flash chromatography (first flash, linear gradient 5 to 7% EtOAc/hexanes, 5 × 25 cm SiO_2; second flash, linear gradient 35 to 50% pentane/benzene, 5 × 15.5 cm SiO_2) afforded 1.78 g (84%) of a clear colorless oil: $[\alpha]^{23}_D$ −43.7° (*c* 1.11, CH_2Cl_2); IR (neat) 2958, 2931, 2857, 1674, 1615, 1587, 1514, 1463 cm^{-1};^{1}H NMR (500 MHz,

$CDCl_3$) δ 7.09 (d, J = 8.5 Hz, 2H), 6.72 (d, J = 8.5 Hz, 2H), 4.58 (q, J = 5.5 Hz, 1H), 4.40 (d, J = 10.3 Hz, 1H), 4.28 (d, J = 10.3 Hz, 1H), 3.89 (dt, J = 5.3, 1.8 Hz, 1H), 3.71 (dd, J = 2.5, 9.3 Hz, 1H), 3.68 (s, 3H), 2.10 (m, 1H), 1.52 (m, 1H), 1.48−1.32 (m, 2H), 1.42 (d, J = 5.5 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.80 (s, 9H), 0.69 (t, J = 7.5 Hz, 3H), 0.64 (d, J = 6.9 Hz, 3H), 0.09 (s, 9H), −0.01 (s, 3H), −0.06 (s, 3H); TLC R_f = 0.80 (20% EtOAc/hexanes). HRMS (FAB) *m*/*z* could not be obtained due to the instability of the product.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(4*S*,5*R*6*S*)-6-[(1*S*,2*S*,3*R*,5*R*,6*S*,-7*R*,8*R*)-8-(*tert*-butyldimethylsiloxy)-2-hydroxy-6-[(*p*-methoxybenzyl)oxy]-1,3,5,7-tetramethyl-4-oxodecyl)]-2,2,5-trimethyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (15). A mixture of 244 mg of silyl enol ether (0.481 mmol) and 319 mg of aldehyde (0.769 mmol) was azeotropically dried twice with 25 mL of benzene before dissolution in 12 mL of CH_2Cl_2. The solution was cooled to −95 °C before 0.591 mL of BF_3·Et_2O (4.81 mmol) was added dropwise down the inside of the flask. Following warming to −78 °C, the solution was stirred for 1.5 h before it was quenched by the addition of ∼3 mL of Et_3N and warmed to ambient temperature. The solution was partitioned between 20 mL of deionized water and 20 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic layers were washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (5 × 11 cm, linear gradient 18 to 35% EtOAc/hexanes followed by 3 × 14.5 cm, linear gradient of 2 to 3% acetone/CH_2Cl_2), affording 333 mg (83%) of a clear colorless oil as a single isolated diastereomer. Data for the isolated diastereomer: $[\alpha]^{23}_D$ −82.1° (*c* 1.2, CH_2Cl_2); IR (neat) 3533, 2935, 2884, 1784, 1695, 1633, 1586, 1514, 1456 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33−7.16 (m, 7H), 6.34 (d, J = 8.5 Hz, 2H), 4.67 (m, 1H), 4.34 (d, J = 10.3 Hz, 1H), 4.30 (d, J = 10.2 Hz, 1H), 4.20 (app t, J = 8.0 Hz, 1H), 4.17 (dd, J = 9.1, 2.7 Hz, 1H), 4.08 (dd, J = 9.7, 1.6 Hz, 1H), 3.98−3.85 (m, 4H), 3.78 (s, 3H), 3.76 (dd, J = 8.7, 1.8 Hz, 1H), 3.21 (dd, J = 13.3, 3.2 Hz, 1H), 3.10 (app quint, J = 6.3, 1H), 2.81 (dq, J = 7.0, 1.0 Hz, 1H), 2.73 (dd, J = 13.3, 9.6 Hz, 1H), 2.57 (d, J = 4.6 Hz, 1H), 1.71 (m, 1H), 1.67−1.45 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H), 1.28 (d, J = 7.0 Hz, 3H), 1.20 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.85−0.70 (m, 12H), 0.08 (s, 3H), 0.06 (s, 3H); TLC R_f = 0.43 (35% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 876.5058, found 876. 5043.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(4*S*,5*R*6*S*)-6-[(1*S*,2*R*,3*S*,4*S*,5*S*,6*R*,-7*R*,8*R*)-8-(*tert*-butyldimethylsiloxy)-2,4-dihydroxy-6-[(*p*-methoxybenzyl)oxy]-1,3,5,7-tetramethyldecyl)]-2,2,5-trimethyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (16). To a solution of 520 mg (0.610 mmol) of aldol adduct in 6 mL of CH_2Cl_2 at 0 °C was added 30 mL (6.10 mmol, 0.20 M in Et_2O) of Zn-$(BH_4)_2$. After 1.0 h, 10 mL each of pH 7 buffer and MeOH was added slowly, and the resultant mixture warmed to ambient temperature and stirred for 12 h. The mixture was extracted by CH_2Cl_2 (3 × 15 mL), and the combined organic extracts were dried over Mg_2SO_4, filtered, and concentrated. The residue was taken up in 50 mL of MeOH and stirred at ambient temperature for 24 h. Following concentration, the residue was partitioned between 20 mL of saturated aqueous NH_4Cl and 20 mL of CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. ^{1}H NMR spectroscopy analysis of the unpurified product showed >98:2 diastereoselectivity. The residue was purified by flash chromatography (3 × 12 cm, linear gradient 20 to 25% EtOAc/hexanes) to afford 492 mg (95%) of a clear colorless oil: $[\alpha]^{23}_D$ −33.6° (*c* 0.25, CH_2Cl_2); IR (neat) 3476, 2936, 2856, 1784, 1695, 1614, 1514, 1 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.10 (m, 7H), 6.83 (d, J = 8.5 Hz, 2H), 4.67 (m, 1H), 4.64 (d, J = 11.1 Hz, 1H), 4.58 (d, J = 11.0 Hz, 1H), 4.20 (app t, J = 9.1, 8.9 Hz, 1H), 4.18 (dd, J = 11.1, 2.7 Hz, 1H), 4.10 (dd, J = 9.3, 1.8 Hz, 1H), 3.98 (m, 1H), 3.90 (dq, J = 3.0, 7.0 Hz, 1H), 3.84 (m, 2H), 3.78 (m, 2H), 3.78 (s, 3H), 3.22 (dd, J = 13.3, 3.2 Hz, 1H), 2.73 (dd, J = 13.4, 9.6 Hz, 1H), 1.88−1.75 (m, 4H), 1.62−1.45 (m, 3H), 1.42 (s, 3H), 1.36 (s, 3H), 1.28 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 0.90 (s, 9H), 0.85−0.72 (m, 15H), 0.08 (s, 3H, 0.06 (s, 3H); TLC R_f = 0.33 (35% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 878.5214, found 878.5223.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(4*S*,5*R*,6*S*)-6-[(1*S*,2*R*,3*R*)-3-[(2*R*,-4*S*,5*S*,6*R*)-6-[(1*R*,2*R*)-2-(*tert*-butyldimethylsiloxy)-1-methylbutyl]-2-(*p*-methoxyphenyl)-5-methyl-*m*-dioxan-4-yl]-2-hydroxy-1-methylbutyl]-2,2,5-trimethyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (17). To mixture of 383 mg (0.448 mmol) of the diol and ∼500 mg Mg_2SO_4 in 4.5 mL of CH_2Cl_2 at ambient temperature was added via cannula an orange solution of 122 mg (0.538 mmol) of DDQ in 5.0 mL of CH_2Cl_2 (followed by a 1 mL rinse) standing over ∼250 mg of Mg_2SO_4. After 10 min, 10 mL of a saturated aqueous $NaHCO_3$ solution was added to the green mixture. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 382 mg (>99%) of a clear, colorless oil which required no further purification: $[\alpha]^{23}_D$ −49.6° (*c* 0.93, CH_2Cl_2); IR (neat) 3522, 3031, 2935, 2856, 1783, 1695, 1615, 1517, 1456 cm^{-1};^{1}H NMR (400 MHz, C_6D_6) δ 7.80 (d, J = 10.0 Hz, 2H), 7.15−6.88 (m, 7H), 6.06 (s, 1H), 4.50 (m, 1H), 4.47 (dd, J = 9.8, 1.9 Hz), 4.33 (m, 1H), 4.26 (m, 1H), 4.22 (dd, J = 10.2, 1.2 Hz, 1H), 4.09 (dd, J = 9.9, 17 Hz, 1H), 3.94 (br, 1H), 3.90 (app d, J = 10.1, 1H), 3.44 (dd, J = 9.1, 2.6 Hz, 1H), 3.32 (s, 3H), 3.16 (app t, J = 8.6 Hz, 1H), 2.99 (dd, J = 13.2, 3.2 Hz, 1H), 2.62 (m, 1H), 2.30 (dd, J = 13.3, 9.5 Hz, 1H), 2.07 (m, 2H), 1.98−1.85 (m, 2H), 1.76 (br d, J = 7.1 Hz, 1H), 1.67−1.49 (m, 2H), 1.60 (d, J = 7.0 Hz, 3H), 1.50 (s, 3H), 1.40 (s, 3H), 1.39 (d, J = 7.0 Hz, 3H), 1.31 (d, J = 7.0 Hz, 3H, 1.18 (d, J = 7.0 Hz, 3H), 1.08 (s, 9H), 0.51 (app t, J = 7.0 Hz, 6H), 0.82 (t, J = 6.0, 3H), 0.20 (s, 3H), 0.14 (s, 3H); TLC R_f = 0.49 (35% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 876.5058, found 876.5050.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(4*S*,5*R*,6*S*)-6-[(1*S*)-1-[(4*R*,5*S*,6*R*)-6-[(1*R*,2*R*,3*R*,4*R*)-4-(*tert*-butyldimethylsiloxy)-2-[(*p*-methoxybenzyl)oxy]-1,3-dimethylhexyl]-2,2,5-trimethyl-*m*-dioxan-4-yl]ethyl]-2,2,5-trimethyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (18). To a solution of 4.2 mg (4.9×10^{-3} mmol) of diol in 1.0 mL of 2,2-dimethoxypropane at ambient temperature was added ∼1 mg of CSA. After 1.0 h, the reaction was quenched by the addition of 5 drops of Et_3N and the resultant solution filtered through a plug of silica. Concentration in vacuo afforded 3.5 mg (80%) of a clear colorless residue: $[\alpha]^{23}_D$ −21.1° (*c* 0.18, CH_2Cl_2); IR (neat) 2933, 2855, 1785, 1695, 1513, 1458 cm^{-1};^{1}H NMR (500 MHz, C_6D_6) δ 7.52 (d, J = 10.0 Hz, 2H), 7.12−7.02 (m, 3H), 6.94 (d, J = 10.0 Hz, 2H), 6.49 (d, J = 10.0 Hz, 2H), 5.01 (d, J = 11.7 Hz, 1H), 4.99 (d, J = 11.8 Hz, 1H), 4.50 (m, 1H, 4.41 (dd, J = 9.8, 1.8 Hz), 4.29 (app d, J = 9.4, 1H), 4.26 (m, 2H), 4.07 (dd, J = 9.9, 1.7 Hz, 1H), 3.82 (dd, J = 6.6, 1.7 Hz, 1H), 3.68 (dd, J = 9.6, 1.7 Hz, 1H), 3.44 (dd, J = 9.9, 2.6 Hz, 1H), 3.18 (app t, J = 8.4 Hz, 1H), 2.98 (dd, J = 13.3, 3.2 Hz, 1H), 2.30 (dd, J = 13.3,

9.5 Hz, 1H), 2.10 (m, 1H), 2.10−2.00 (m, 2H), 1.98 (m, 1H), 1.86 (app q, J = 6.7 Hz, 1H), 1.70 (m, 1H), 1.68 (s, 3H), 1.62 (m, 1H), 1.58 (d, J = 7.0 Hz, 3H), 1.53 (s, 3H), 1.52 (s, 3H), 1.45 (s, 3H), 1.19 (d, J = 7.0 Hz, 3H), 1.16 (s, 9H), 1.15 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 7.0 Hz, 3H), 1.00 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.0 Hz, 3H), 0.90 (t, J = 6.0, 3H), 0.26 (s, 3H,), 0.19 (s, 3H); TLC R_f = 0.48 (20% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 918.5527, found 918.5512.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(4*S*,5*R*,6*R*)-6-[(1*S*,2*R*,3*R*)-3-[(2*R*,-4*S*,5*S*,6*R*)-6-[(1*R*,2*R*)-2-(*tert*butyldimethylsiloxy)-1-methylbutyl]-2-(*p*-methoxyphenyl)-5-methyl-*m*-dioxan-4-yl]-2-hydroxy-1-methylbutyl]-2,2,5-trimethyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone, methyl dithiocarbonate (19). To a solution of 82.5 mg (0.0967 mmol) of alcohol in 3.2 mL of THF at 0 °C was added >5 mg of 95% NaH, followed by freshly distilled CS_2 (58.2 μL, 0.967 mmol). The resultant gray suspension was stirred for 1 h at 0 °C and 1 h at ambient temperature. The reaction was then recooled to 0 °C before 0.250 mL (4.02 mmol) of methyl iodide was added via syringe. After 4 h at 0 °C, the reaction was warmed to ambient temperature and allowed to stir for 12 h. At that time, an addition 1 mL (16.1 mmol) of methyl iodide was added to the slightly yellow solution, and the reaction permitted to proceed for an additional 12 h. The reaction was partitioned between 2 mL of CH_2Cl_2 and 5 mL of H_2O, and the aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford a yellow oil. Purification by flash chromatography (linear gradient 10 to 20% EtOAc/hexanes, 2 × 10.5 cm SiO_2) yielded 76.2 mg (84%) of a pale yellow oil: $[\alpha]^{23}_D$ −42.5° (*c* 1.00, CH_2Cl_2); IR (neat) 2970, 2933, 2880, 2855, 1784, 1694, 1516 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.18 (m, 7H), 6.87 (d, J = 10.0 Hz, 2H), 6.13 (d, J = 2.7 Hz, 1H), 5.52 (s, 1H), 4.69 (m, 1H), 4.22 (app t, J = 7.7 Hz, 1H), 4.18 (dd, J = 9.1, 2.8 Hz, 1H), 4.06 (dd, J = 9.8, 1.9 Hz, 1H), 4.00 (ddd, J = 1.2, 7.5, 8.7 Hz, 1H), 3.94 (d, J = 11.3 Hz, 1H), 3.91 (dq, J = 6.8, 9.7 Hz, 1H), 3.87 (dd, J = 10.2, 1.9 Hz, 1H), 3.78 (s, 3H), 3.59 (dd, J = 10.1, 2.0 Hz, 1H), 3.22 (dd, J = 13.3, 3.3 Hz, 1H), 2.73 (dd, J = 13.4, 9.6 Hz, 1H), 2.65 (m, 1H), 2.55 (s, 3H), 1.91 (m, 1H), 1.67 (m, 2H,), 1.59 (m, 1H), 1.49 (m, 2H), 1.33 (s, 6H), 1.29 (d, J = 7.0 Hz, 3H), 1.18 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 7.0 Hz, 3H), 0.87 (s, 9H), 0.79 (t, J = 6.0, 3H), 0.75 (d, J = 7.0 Hz, 3H), 0.74 (d, J = 7.0 Hz, 3H), 0.01 (s, 3H), −0.01 (s, 3H); TLC R_f = 0.78 (35% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 966.4656, found 966.4652.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(4*S*,5*R*,6*S*)-6-[(1*S*,3*R*)-3-[(2*R*,4*S*,-5*S*,6*R*)-6-[(1*R*,2*R*)-2-(*tert*-butyldimethylsiloxy)-1-methylbutyl]-2-(*p*-methoxyphenyl)-5-methyl-*m*-dioxan-4yl]-1-methylbutyl]-2,2,5-trimethyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (20). Azeotropically dried (benzene) xanthate (127 mg, 0.134 mmol) was taken up in 2.5 mL of tributyltin hydride and heated to 110 °C before a catalytic amount of AIBN was added. After 30 min, the reaction was cooled to ambient temperature and quenched by the addition of 3 mL of H_2O. The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford a clear colorless liquid which was first purified by filtration through SiO_2 (hexanes followed by 50% EtOAc/hexanes, 3 × 10.5 cm SiO_2). The unpurified reaction mixture was then dissolved in 5 mL of CH_2Cl_2 and treated with a catalytic amount of CSA for 12 h prior to purification by flash chromatography (linear gradient 0.5 to 1.0% acetone/CH_2Cl_2, 3 × 7.5 cm SiO_2) to afford a 94.3 mg (84%) of a clear colorless foam as a single isomer: $[\alpha]^{23}_D$ −51.7° (*c* 1.00, CH_2Cl_2); IR (neat) 2960, 2934, 1786, 1695, 1517 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43−7.18 (m, 7H), 6.87 (d, J = 10.0 Hz, 2H), 5.59 (s, 1H), 4.69 (m, 1H), 4.22 (app t, J = 7.7, 9.2 Hz, 1H), 4.17 (dd, J = 9.1, 2.7 Hz, 1H), 4.05 (dd, J = 9.7, 1.9 Hz, 1H), 4.00 (ddd, J = 5.9, 0.9, 7.8 Hz, 1H), 3.90 (dd, J = 9.6, 2.8 Hz, 1H), 3.90 (m, 1H), 3.78 (s, 3H), 3.33 (dd, J = 9.7, 2.0 Hz, 1H), 3.32 (d, J = 11.0 Hz, 1H), 3.22 (dd, J = 13.3, 3.3 Hz, 1H), 2.74 (dd, J = 13.3, 9.8 Hz, 1H), 2.22 (m, 1H), 2.01 (m, 1H), 1.73−1.66 (m, 2H), 1.61 (m, 1H), 1.47 (m, 2H, 1.39 (s, 3H), 1.34 (s, 3H), 1.29 (d, J = 6.8 Hz, 3H), 1.15 (d, J = 7.0 Hz, 3H), 1.08 (d, J = 7.0 Hz, 3H), 0.8−0.6 (m, 2H), 0.87 (s, 9H), 0.82 (d, J = 7.0 Hz, 3H), 0.80 (t, J = 6.0, 3H), 0.75 (d, J = 7.0 Hz, 3H), 0.74 (d, J = 7.0 Hz, 3H), 0.01 (s, 3H), −0.01 (s, 3H); 7; TLC R_f = 0.70 (5% acetone/CH_2Cl_2). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 860.5109, found 860.5144.

(4*S*,5*R*,6*S*)-6-[(1*S*,3*R*)-3-[(2*R*,4*S*,5*S*,6*R*)-6-[(1*R*,2*R*)-2-(*tert*-butyldimethylsiloxy)-1-methylbutyl]-2-(*p*-methoxyphenyl)-5-methyl-*m*-dioxan-4yl]-1-methylbutyl]-4-[(1*R*)-1-carboxyeth-1-yl]-2,2,5-trimethyl-*m*-dioxane (20a). To a solution of 40.0 mg (0.0478 mmol) of imide in 2.5 mL of THF and 0.5 mL of H_2O at 0 °C was added 0.0433 mL (0.382 mmol) of a 30% aqueous solution of H_2O_2 followed by 0.478 mL (0.0956 mmol) of a 0.2 M aqueous solution of LiOH. After 1 h, the solution was warmed to ambient temperature and stirred for 4 h. The reaction was then recooled to 0 °C before treatment with 2 mL of a 1.5 M Na_2SO_3 aqueous solution. After 15 min, the reaction was diluted with 5 mL of Et_2O and then acidified to pH 1 with 1 M HCl. The aqueous layer was isolated, and extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford an oil. The residue was purified by flash chromatography (linear gradient 25 to 35% EtOAc/hexanes, 1 × 12 cm SiO_2), to obtain 23.2 mg (72%) of a clear colorless oil: $[\alpha]^{23}_D$ −31.3° (*c* 0.989, CH_2Cl_2); IR (neat) 2957, 2932, 1710, 1616, 1517 cm^{-1};^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, J = 10.0 Hz, 2H), 6.87 (d, J = 10.0 Hz, 2H), 5.52 (s, 1H), 4.00 (app t, J = 7.7 Hz, 1H), 3.90 (dd, J = 10.1, <1.0 Hz, 1H), 3.83 (dd, J = 9.5, 1.1 Hz, 1H), 3.78 (s, 3H), 3.33 (d, J = 11.0 Hz, 1H), 3.28 (dd, J = 12.2, 1.8 Hz, 1H), 2.64 (dq, J = 6.9, 9.5 Hz, 1H), 2.22 (m, 1H), 1.99 (m, 1H), 1.67 (m, 2H), 1.58 (m, 1H), 1.49 (m, 2H), 1.38 (s, 3H), 1.35 (s, 3H), 1.22 (d, J = 7.0 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 7.0 Hz, 3H), 0.89 (s, 9H), 0.87−0.72 (m, 12H), 0.8−0.6 (m, 2H), 0.01 (s, 3H), −0.01 (s, 3H); TLC R_f = 0.69 (50% EtOAc/hexane). HRMS (FAB$^-$) *m*/*z* calcd for [M − H]$^-$ 677.4449, found 677.4431.

(4*S*,5*R*,6*S*)-4-[(1*R*)-1-Carboxyeth-1-yl]-6-[(1*S*,3*R*)-3-[(2*R*,-4*S*,5*S*,6*S*)-6-[(1*S*,2*R*)-2-(hydroxy)-1-methylbutyl]-2-(*p*-methoxyphenyl)-5-methyl-*m*-dioxan-4yl]-1-methylbutyl]-2,2,5-trimethyl-*m*-dioxane (23). To a solution of 23.2 mg (0.0342 mmol) of silyl ether in 0.68 mL of THF at 0 °C was added 0.0513 mL of a 1.0 M HF-purified TBAF solution in THF. The resultant clear yellow solution was gradually warmed to 65 °C and maintained at that temperature for 10 h before the reaction was quenched by the addition of 2.0 mL of a saturated aqueous solution of NH_4Cl. Following dilution with 3 mL of Et_2O, the layers were separated and the aqueous layer extracted with Et_2O (5 × 3 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (50% EtOAc/hexanes to 50% EtOAc/hexanes with one drop acetic acid/100 mL eluant, 1 × 10.5 cm SiO_2) to afford 17.0 mg (88%) of clear

colorless oil. This compound was carried on directly to macrocyclization: IR (neat) 3449, 3500−2300 (broad), 3052, 2967, 2935, 2878, 1714, 1616, 1517, 1459 cm^{-1}.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-13-Ethyl-9,11-[(*R*)−(*p*-methoxybenzylidene)dioxy]-3,5-[(1-methylethylidene)-dioxy]-2,4,6,8,10,12-hexamethyltetradecanolide (24). To a solution of 29.2 mg (0.0518 mmol) of azeotropically dried (2 × 5 mL of benzene) hydroxy acid in 5.18 mL of benzene at room temperature was added 90.2 μL (0.518 mmol) of Hünig's base, followed by 40.4 μL (0.259 mmol) of 2,4,6-trichlorobenzoyl chloride. After 1 h, an additional 90.2 μL of Hünig's base and 80.8 μL (0.518 mmol) of 2,4,6-trichlorobenzoyl chloride were added. After 4 h, 253 mg (2.08 mmol) of *N*,*N*-(dimethylamino)pyridine was added as well as 5 mL of benzene, resulting in precipitation of a dense white solid. After 45 min, the reaction was treated with 10 mL of a 1 *N* aqueous solution of $NaHSO_4$ and 10 mL of CH_2Cl_2. Upon separation, the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (1 × 5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The product was purified by flash chromatography (linear gradient 2.5 to 5.0% EtOAc/hexanes, 1 × 8 cm SiO_2) to afford 25.0 mg (86%) of a clear colorless oil: $[\alpha]^{23}_D$ +11.0° (*c* 0.060, CH_2Cl_2); IR (neat) 2960, 2936, 2877, 1721, 1616, 1518 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.69 (s, 1H), 5.43 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.94 (d, *J* = 6.9 Hz, 1H), 3.81 (d, *J* = 10.9 Hz, 1H), 3.78 (s, 3H), 3.61 (d, *J* = 9.5 Hz, 1H), 3.37 (d, *J* = 10.6 Hz, 1H), 2.73 (dq, *J* = 10.8, 6.7 Hz), 2.34 (m, 1H), 2.18 (m, 1H), 1.89 (q, *J* = 6.8 Hz, 1H), 1.69 (m, 4H), 1.48 (s, 3H), 1.45 (s, 3H), 1.42−1.30 (m, 2H), 1.20 (d, *J* = 7.0 Hz, 3H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 6H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.88 (app t, *J* = 6.8 Hz, 6H); TLC R_f = 0.74 (35% EtOAc/hexane); HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 547.3635, found 547.3644.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,9*S*,10*S*,11*R*,12*R*,13*R*)-13-Ethyl-9,11-dihydroxy-3,5-[(1-methylethylidene)dioxy]-2,4,6,8,10,12-hexamethyltetradecanolide (25). To a solution of 53.4 mg (0.102 mmol) of acetal in 1.0 mL of 2-propanol at ambient temperature was added ∼10 mg of $Pd(OH)_2$. The flask was subsequently purged for 5 min with H_2 under balloon pressure and then maintained under positive pressure (balloon). After 13 h, the mixture was filtered through a plug of Celite with 10 mL of EtOAc and concentrated in vacuo. The product was purified by flash chromatography (20% EtOAc/hexanes, 1 × 15 cm SiO_2) to afford 38.8 mg (89%) of the diol (the remainder of the material as the tetraol which could be recycled to give 99% yield): $[\alpha]^{23}_D$ +38.1° (*c* 0.200, CH_2Cl_2); IR (neat) 3392, 2973, 2937, 2871, 1728, 1456 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.22 (dd, *J* = 9.3, 4.4 Hz, 1H), 3.85 (d, *J* = 6.2 Hz, 1H), 3.70 (d, *J* = 10.7 Hz, 1H), 3.65 (d, *J* = 10.0 Hz, 1H), 3.05 (dd, *J* = 9.9, 2.2 Hz, 1H), 2.74 (dq, *J* = 6.5, 10.6 Hz, 1H), 2.13 (m, 1H), 1.94 (q, *J* = 7.1 Hz, 1H), 1.78−1.64 (m, 3H), 1.47 (m, 2H), 1.42 (s, 6H), 1.30−1.10 (m, 2H), 1.18 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 6H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.4 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H); TLC R_f = 0.47 (35% EtOAc/hexane); HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 451.3035, found 451.3040.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,10*R*,11*S*,12*R*,13*R*)-13-Ethyl-11-hydroxy-3,5-[(1-methylethylidene)dioxy]-2,4,6,8,10,12-hexamethyl-9-oxotetradecanolide (25a). To a solution 25.0 mg (0.0585 mmol) of diol in 1 mL of CH_2Cl_2 at room temperature was added ∼100 mg of 4 Å sieves followed by 50.0 mg (0.234 mmol) of PCC. After 1 h of stirring, the green/brown mixture was filtered through Celite with 10 mL of EtOAc and concentrated in vacuo. The brown residue was immediately purified by flash chromatography (15% EtOAc/hexanes, 1 × 16 cm SiO_2) to afford 18.9 mg (76%) of a clear colorless oil: $[\alpha]^{23}_D$ −51.8° (*c* 0.975, CH_2Cl_2); IR (neat) 3480, 2975, 2839, 2881, 1724, 1707, 1457 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 5.29 (ddd, *J* = 9.4, 4.4, 1.3 Hz, 1H), 3.95 (dd, *J* = 2.2, 10.0 Hz, 1H), 3.90 (dd, *J* = 0.9, 6.4 Hz, 1H), 3.76 (dd, *J* = 10.6, <1.0 Hz, 1H), 2.79 (m, 2H), 2.63 (m, 1H), 2.12 (m, 1H), 1.87 (q, *J* = 6.6 Hz, 1H), 1.78 (m, 1H), 1.67 (m, 2H), 1.50 (m, 1H), 1.44 (s, 6H), 1.22 (m, 1H), 1.17 (d, *J* = 6.5 Hz, 3H), 1.05 (d, *J* = 6.6 Hz, 3H), 1.02 (d, *J* = 6.3 Hz, 3H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.7 Hz, 3H); TLC R_f = 0.84 (35% EtOAc/hexane); HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 449.2879, found 449.2893.

6-Deoxyerythronolide B (1). To a solution of 18.9 mg (0.0444 mmol) in 1.0 mL of THF was added 5 drops of a 1 M HCl aqueous solution. The resultant solution was stirred at room temperature for 4 h, before the reaction was partitioned between 5 mL of H_2O and 5 mL of Et_2O. The organic layer was separated and washed with a saturated aqueous soution of $NaHCO_3$ (1 × 5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash chromatography (30% EtOAc/hexanes, 1 × 15 cm SiO_2) afforded 16.0 mg (94%) of a white powder: $[\alpha]^{23}_D$ −38.9° (*c* 0.800, CH_2Cl_2); IR (neat) 3477, 2974, 2933, 1703, 1456 cm^{-1};^1H NMR (400 MHz, $CDCl_3$) δ 5.14 (ddd, *J* = 1.1, 4.0, 9.6 Hz, 1H), 3.99 (ddd, *J* = 1.7, 3.4, 4.8 Hz, 1H), 3.91 (ddd, *J* = <1.0, 2.8, 10.3 Hz, 1H), 3.87 (d, *J* = 4.4 Hz, 1H), 3.67 (ddd, *J* = 4.4, 2.0, 10.2 Hz, 1H), 3.02 (d, *J* = 2.8 Hz, 1H), 2.78 (m, 2H), 2.62 (m, 1H), 2.25 (d, *J* = 3.4 Hz, 1H), 2.02 (m, 1H), 1.86 (dq, *J* = 1.7, 6.2 Hz, 1H, 1.82 (m, 1H), 1.73 (m, 1H), 1.67 (m, 1H), 1.51 (m, 1H), 1.29 (d, *J* = 6.7 Hz, 3H), 1.25 (m, 1H), 1.06 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 6.4 Hz, 3H), 1.04 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H); TLC R_f = 0.27 (35% EtOAc/hexanes); HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 409.2566, found 409.2559.

(4*R*)-4-Benzyl-3-[(2*S*)-4-bromo-2-methyl-1-oxo-4-pentenyl]-2-oxazolidinone (27). To a solution of 11.8 mL (90.0 mmol) of diisopropylamine in 81 mL of THF at −78 °C was added 32.4 mL (81.0 mmol) of a 2.5 M solution of *n*-butyllithium in hexanes. After 30 min, the yellow solution was treated with a solution of 17.5 g (75.0 mmol) of imide in 19.5 mL of THF (with 2 × 3-mL rinses) via cannula. After 40 min at −78 °C, 29 mL (282 mmol) of 2,3-dibromopropene was added neat via syringe. The resultant dark brown/black solution was warmed to −35 °C and maintained at that temperature for 14 h. The reaction was quenched with 50 mL of saturated aqueous NH_4Cl, and the solution was partitioned between 20 mL of H_2O and 100 mL of 25% CH_2Cl_2/pentane. The organic layer was washed with 1 M HCl (1 × 100 mL) and brine (1 × 100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (50% CH_2Cl_2/hexanes, 10 × 24 cm SiO_2), to afford 20.5 g (79%) of a clear colorless oil: $[\alpha]^{23}_D$ −39.1° (*c* 1.01, CH_2Cl_2); IR (neat) 3068, 3026, 2974, 2933, 1780, 1733, 1697, 1631 cm^{-1};^1H NMR (500 MHZ, $CDCl_3$) δ 7.35−7.20 (m, 5H), 5.69 (s, 1H), 5.50 (s, 1H), 4.69 (m, 1H), 4.21 (app t, *J* = 7.9 Hz, 1H), 4.19 (m, 1H), 4.17 (dd, *J* = 3.0, 9.1 Hz, 1H), 3.28 (dd, *J* = 13.4, 3.2 Hz, 1H), 3.01 (dd, *J* = 7.6, 14.5 Hz, 1H), 2.75 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.53 (dd, *J* = 6.7, 14.5 Hz, 1H), 1.22 (d, *J* = 6.9

Hz, 3H); TLC $R_f = 0.62$ (33% hexanes/CH_2Cl_2). HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 374.0368, found 374.0372.

(4*R*)-4-Benzyl-3-[(2*R*,4*R*,5*S*,6*S*)-8-bromo-5-hydroxy-2,4,6-trimethyl-1,3-dioxo-8-nonenyl]-2-oxazolidinone (29). To a clear solution of $TiCl_4$ (4.78 mL, 43.6 mmol) in CH_2Cl_2 (560 mL) at 0 °C was added Ti(*i*-OPr)$_4$ (4.33 mL, 14.5 mmol). After 15 min, a solution of 16.24 g (56.2 mmol) of β-keto imide in 20.0 mL of CH_2Cl_2 was added via cannula (1 × 10 mL rinse). To the resultant yellow solution was added Et_3N (8.36 mL, 60.0 mmol), affording instantly a dark red solution which was stirred at 0 °C for 1 h. The reaction was then cooled to −78 °C before a solution of 6.63 g (37.5 mmol) mL of aldehyde in 10 mL of CH_2Cl_2 was added via cannula, and the reaction was stirred at −78 °C for 45 min. The reaction was quenched by the addition of 200 mL of a saturated aqueous NH_4Cl solution at −78 °C and warmed to ambient temperature. The mixture was diluted with 100 mL of H_2O and 700 mL of Et_2O. The layers were separated, and the aqueous layer was extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (1 × 200 mL), dried over Na_2SO_4, and concentrated in vacuo to afford a yellow clear oil. Analysis of the unpurified reaction mixture by ^{1}H NMR revealed a >95:5 ratio of diastereomers with complete consumption of the aldehyde. This residue was purified by flash chromatography (linear gradient 15 to 25% EtOAc/hexanes) to afford 16.78 g (96%) of a single diastereomer as a clear colorless oil: $[\alpha]^{23}_D$ −131.1° (*c* 1.04, CH_2Cl_2); IR (neat) 3529, 3026, 2974, 2944, 1769, 1713, 1692 cm^{-1}; ^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.38−7.16 (m, 5H), 5.58 (t, J = 1.3 Hz, 1H), 5.45 (s, 1H), 4.84 (q, J = 7.1 Hz, 1H), 4.76 (m, 1H), 4.28 (app t, J = 8.3 Hz, 1H), 4.19 (dd, J = 3.1, 9.1 Hz, 1H), 3.84 (ddd, J = 9.5, 3.2, 1.6 Hz, 1H), 3.28 (dd, J = 13.4, 3.3 Hz, 1H), 3.07 (dd, J = <1.0, 12.0 Hz, 1H), 3.03 (dq, J = 1.6, 7.0 Hz, 1H), 2.90 (d, J = 3.2 Hz, 1H), 2.78 (dd, J = 13.4, 9.4 Hz, 1H), 2.12 (dd, J = 14.3, 10.3 Hz, 1H), 1.96 (m, 1H, C_6-*H*), 1.47 (d, J = 7.3 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.7 Hz, 3H); TLC $R_f = 0.11$ (20% EtOAc/hexanes). HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 488.1049, found 488.1072.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*,5*S*,6*S*)-8-bromo-3,5-dihydroxy-2,4,6-trimethyl-1-oxo-8-nonenyl]-2-oxazolidinone (29a). To a clear yellow solution of purified aldol adduct (69.2 mg, 0.148 mmol) in 3.0 mL of CH_2Cl_2 at −78 °C was added a solution of $Zn(BH_4)_2$ in Et_2O (1.90 mL, 0.15 M solution). The resultant clear solution was stirred for 15 min at −78 °C before the reaction was warmed to −50 °C and maintained at that temperature for 1.5 h. The reaction was then treated with 5 mL of a saturated aqueous solution of NH_4Cl at −50 °C. The mixture was stirred vigorously as it was warmed to ambient temperature. After 10 min at ambient temperature, the mixture was diluted with 4 mL of CH_2Cl_2 and 2 mL of brine, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (1 × 4 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resultant clear colorless oil was azeotroped with MeOH (5 × 5 mL) followed by heptane (1 × 5 mL). Analysis of the unpurified material by ^{1}H NMR revealed a >95:5 ratio of diastereomers. The product was purified by flash chromatography (35% EtOAc/hexanes, 1 × 12.5 cm SiO_2), to afford 61.7 mg (89%) of a clear colorless oil: $[\alpha]^{23}_D$ −64.4° (*c* 1.16, CH_2Cl_2); IR (neat) 3456, 3067, 3026, 2974, 2933, 1764, 1692, 1631 cm^{-1};^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.37−7.19 (m, 5H), 5.59 (s, 1H), 5.45 (s, 1H), 4.69 (m, 1H), 4.24 (app t, J = 9.1 Hz, 1H), 4.19 (dd, J = 2.9, 9.1 Hz, 1H), 4.00 (m, 2H), 3.45 (dd, J = <1.0, 9.1 Hz, 1H), 3.24 (dd, J = 13.4, 3.2 Hz, 1H), 2.98 (dd, J = 2.6, 14.3 Hz, 1H), 2.78 (dd, J = 13.4, 9.5 Hz, 1H), 2.11 (dd, J = 14.1, 10.0 Hz, 1H), 1.96 (m, 1H), 1.81 (m, 1H), 1.28 (d, J = 6.6 Hz, 3H), 0.98 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H); TLC R_f = 0.17 (35% EtOAc/hexanes). HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 490.1205 found 490.1227.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*)-3-bromo-1-methyl-3-butenyl]-5-methyl-2-phenyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (30). To a solution of 0.7505 g of diol (1.60 mmol) in 1.20 mL of benzaldehyde dimethyl acetal (8.02 mmol) was added a catalytic amount of CSA. The resultant mixture was stirred at ambient temperature under vacuum (∼10 Torr) for 10 h before it was loaded directly on a column and purified by flash chromatography (linear gradient 10 to 15% EtOAc/hexanes, 5 × 13.5 cm SiO_2) to afford 0.7554 g (79%) of a clear colorless foam: $[\alpha]^{23}_D$ −61.1° (*c* 1.05, CH_2Cl_2); IR (solution, CH_2Cl_2) 3068, 2973, 2934, 1782, 1695, 1629 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55−7.19 (m, 10H), 5.60 (s, 1H), 5.55 (s, 1H), 5.47 (s, 1H), 4.74 (m, 1H), 4.25 (app t, J = 9.1 Hz, 1H), 4.22 (dd, J = 2.9, 9.1 Hz, 1H), 4.13 (m, 2H), 3.54 (dd, J = 1.8, 9.6 Hz, 1H), 3.26 (dd, J = 13.3, 3.2 Hz, 1H), 3.05 (d, J = 12.9 Hz, 1H), 2.78 (dd, J = 13.3, 9.6 Hz, 1H), 2.19 (dd, J = 13.7, 9.9 Hz, 1H), 2.12 (m, 1H), 1.86 (q, J = 6.9 Hz, 1H), 1.43 (d, J = 6.1 Hz, 3H), 0.93 (d, J = 6.9 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H); TLC R_f = 0.39 (20% EtOAc/hexanes). HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 578.1518, found 578.1534.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(2*S*,4*S*,5*R*,6*S*)-5-methyl-6-[(1*S*)-1-methyl-3-(trimethylstannyl)-3-butenyl]-2-phenyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (31). To a solution of 755.4 mg (1.36 mmol) of vinyl bromide in 14 mL of benzene at room temperature were added 0.049 mL (0.272 mmol) of Hünig's base and 0.810 mL (2.73 mmol) of hexamethylditin via syringe, followed by 78.6 mg (0.0680 mmol) of tetrakis(triphenylphosphine)palladium. The resultant yellow solution was heated to 80 °C, gradually darkening to a black color. After 1 h at 80 °C, the reaction was cooled to ambient temperature and stirred for an additional 2 h. The reaction was quenched by the addition of 10 mL of a saturated aqueous solution of Cu_2SO_4. The mixture was extracted with hexanes (1 × 10 mL). The organic layer was then washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4, filtered through Celite with 20 mL of EtOAc, and concentrated in vacuo to provide a yellow oil. The product was purified by flash chromatography (10% EtOAc/hexanes, 5 × 10 cm SiO_2) to afford 777.3 mg (90%) of a clear colorless foam: $[\alpha]^{23}_D$ −54.9° (*c* 1.00, CH_2Cl_2); IR (neat) 3031, 2970, 2932, 1785, 1696 cm^{-1};^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.46 (d, J = 6.8 Hz, 2H), 7.33−7.20 (m, 6H), 7.17 (d, J = 6.8 Hz, 2H), 7.17 (d, J = 7.0 Hz, 2H), 5.67 (ddt, J = 1.7, 2.2, 76.2 Hz, 1H), 5.57 (s, 1H), 5.22 (ddt, J = 1.4, 2.9, 35.4 Hz, 1H), 4.73 (m, 1H), 4.24 (app t, J = 9.1 Hz, 1H), 4.20 (dd, J = 3.0, 9.1 Hz, 1H), 4.14 (m, 2H), 3.48 (dd, J = 2.0, 9.7 Hz, 1H), 3.27 (dd, J = 13.3, 3.3 Hz, 1H), 3.07 (d, J = 13.0 Hz, 1H), 2.78 (dd, J = 13.3, 9.5 Hz, 1H), 1.87 (dd, J = 12.9, 10.7 Hz, 1H), 1.85 (m, 1H), 1.74 (m, 1H), 1.44 (d, J = 6.2 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 0.77 (d, J = 6.6 Hz, 3H), 0.14 (dt, J = 1.2, 26.4 Hz, 9H); TLC R_f = 0.41 (20% EtOAc/hexanes). HRMS (FAB) *m/z* calcd for $[M + Na]^+$ 664.2061, found 664.2076.

(4*R*)-4-Benzyl-3-[(2*R*,4*S*,5*R*)-5-hydroxy-2,4-dimethyl-1,3-dioxohexyl]-2-oxazolidinone (32). To a suspension of 35.8 g (86.0 mmol) of stannous triflate in 287 mL of CH_2Cl_2 at ambient temperature was added 12.5 mL (89.7 mmol) of Et_3N. The resultant pale yellow slurry was then cooled immediately to −20 °C and stirred for 5 min before a solution of 21.6 g (74.7 mmol) of β-keto imide in 50 mL of CH_2Cl_2 was added via cannula over 10 min. The resultant nearly homogeneous solution was stirred at −20 °C for 1 h. The reaction was then cooled to

−78 °C and treated with 5.01 mL (89.7 mmol) of freshly distilled acetaldehyde. After 30 min of stirring at −78 °C, the reaction was rapidly added via cannula to a vigorously stirring mixture of 1.5 L of CH_2Cl_2 and 1.5 L of 1 *N* $NaHSO_4$ at 0 °C. The mixture was stirred for 30 min until both layers became clear, whereupon the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 500 mL). The combined organics were washed with a saturated solution of $NaHCO_3$ (1 × 500 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo to afford 25.1 g (100%) of a clear colorless oil. The unpurified mixture was analyzed by ^{1}H NMR to reveal a 83:17 ratio of diastereomers. The mixture could not be purified by flash chromatography or HPLC without concomitant epimerization and lactonization, and was therefore carried on without further purification. [TLC R_f = 0.19 (35% EtOAc/hexanes).]

(4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*S*,5*R*)-3,5-dihydroxy-2,4-dimethyl-1-oxohexyl]-2-oxazolidinone (32a). To 2.0 L of acetic acid maintained between 0 and 25 °C was added portionwise 28.3 g (747 mmol) of $NaBH_4$. Upon completion of gas evolution, the reaction was allowed to warm to ambient temperature where it was stirred for 1.5 h. To this solution was added via cannula a solution of 25.1 g (74.7 mmol) of aldol adduct in 500 mL of acetic acid over the course of 20 min. After an additional 15 min, the reaction was concentrated in vacuo before it was partitioned between 500 mL of H_2O and 500 mL of CH_2Cl_2. The aqueous layer was separated and extracted by CH_2Cl_2 (3 × 300 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (1 × 500 mL). The aqueous layer was extracted by CH_2Cl_2 (3 × 300 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was then azeotroped with MeOH (3 × 500 mL) with the addition of 1 mL of acetic acid during the first round, and with heptane (2 × 500 mL), to obtain 25.0 g (100%) of a clear colorless foam that could not be further purified without concomitant lactonization. [TLC R_f = 0.05 (35% EtOAc/hexanes).]

(4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*,5*R*)-3-hydroxy-5-(triisopropylsiloxy)-2,4-dimethyl-1-oxohexyl]-2-oxazolidinone (33). To a solution of 25.0 g (74.7 mmol) diol in 1.5 L CH_2Cl_2 at −5 °C was added 10.44 mL (89.6 mmol) of 2,6-lutidine, followed by 22.12 mL (82.2 mmol) of TIPSOTf. The resultant clear colorless solution was stirred at −5 °C for 1 h before the addition of 500 mL of a saturated solution of aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 200 mL). The combined organics were washed with 1 *N* $NaHSO_4$ (1 × 200 mL), H_2O (1 × 200 mL), and brine (1 × 200 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The major isomer was purified by flash chromatography (20% Et_2O/hexanes, 11 × 23 cm SiO_2) to yield 26.6 g (73%) of a clear colorless oil: $[\alpha]^{23}_D$ −16.8° (*c* 1.52, CH_2Cl_2); IR (neat) 3451, 2943, 2867, 1782, 1703 cm^{-1}; ^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.36−7.17 (m, 5H), 4.68 (m, 1H), 4.61 (s, 1H), 4.20 (app t, *J* = 7.5 Hz, 1H), 4.13 (dd, *J* = 9.3, 2.2 Hz, 1H), 4.12 (m, 1H), 4.07 (dd, *J* = 1.9, 10.1 Hz, 1H), 3.84 (dq, *J* = 2.0, 6.8 Hz, 1H), 3.35 (dd, *J* = 13.2, 3.0 Hz, 1H), 2.73 (dd, *J* = 13.2, 9.9 Hz, 1H), 1.93 (m, 1H), 1.23 (d, *J* = 6.4 Hz, 3H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.05 (s on top of m, 21H), 0.82 (d, *J* = 7.1 Hz, 3H); TLC R_f = 0.84 (35% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 514.2965, found 514.2968.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*R*,5*R*)-3-(benzyloxy)-5-(triisopropylsiloxy)-2,4-dimethyl-1-oxohexyl]-2-oxazolidinone (34). To a solution of 2.16 g (4.41 mmol) of alcohol in 14.7 mL of CH_2Cl_2 at ambient temperature was added 1.00 mL (5.29 mmol) of benzyl trichloroacetimidate, followed by 44 drops of an ethereal TfOH solution (1 drop of neat triflic acid in 1 mL of Et_2O). The resultant yellow solution was stirred at ambient temperature for 1 h, during which time a white solid gradually precipitated out of the reaction mixture. At this time an additional 0.250 mL (1.32 mmol) of acetimidate was added. After 1 h, an additional drop of neat triflic acid was added. The reaction was quenched after a total of 3 h by the addition of 10 mL of a solution of saturated $NaHCO_3$, and the layers were separated. The aqueous phase was extracted by CH_2Cl_2 (1 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was then taken up in hexane, and the white flocculent solid was filtered off and rinsed with hexanes (10 × 5 mL). After concentration of the filtrate, a pale yellow oil was obtained. The product was purified by flash chromatography (7.5 to 10% EtOAc/hexanes, 8 × 14 cm SiO_2), affording 2.14 g (84%) of a clear colorless oil: $[\alpha]^{23}_D$ −44.4° (*c* 1.42, $CHCl_3$); IR (solution, CH_2Cl_2) 3029, 2944, 2867, 1782, 1701 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.22 (m, 10H), 4.58 (d, *J* = 10.5 Hz, 1H), 4.47 (m, 1H), 4.45 (d, *J* = 10.5 Hz, 1H), 4.42 (dq, *J* = 2.0, 6.4 Hz, 1H), 4.16 (dd, *J* = 9.1, 2.0 Hz, 1H), 4.09 (app t, *J* = 7.5 Hz, 1H), 4.06 (dq, *J* = 2.8, 6.8 Hz, 1H), 3.97 (dd, *J* = 2.8, 9.1 Hz, 1H), 3.35 (dd, *J* = 13.3, 3.1 Hz, 1H), 2.78 (dd, *J* = 13.3, 9.8 Hz, 1H), 1.60 (m, 1H), 1.27 (d, *J* = 6.8 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 3H), 1.08 (s on top of m, 21H), 0.97 (d, *J* = 7.0 Hz, 3H); TLC R_f = 0.44 (20% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 604.3434, found 604.3427.

(2*R*,3*S*,4*R*,5*R*)-3-(Benzyloxy)-5-(triisopropylsiloxy)-2,4-dimethylhexanoic acid (34a). To a solution of 5.11 g (8.79 mmol) of imide in 176 mL of THF at 0 °C was added 2.39 mL (7.03 mmol) of a 30% aqueous solution of H_2O_2 followed by 88.0 mL (17.6 mmol) of a 0.2 M aqueous solution of LiOH. The resultant clear colorless solution was stirred at 0 °C for 6 h before it was quenched by the addition of 150 mL of a 1.5 M aqueous solution of Na_2SO_3. The mixture was stirred vigorously at 0 °C. After 30 min, the mixture was extracted by Et_2O (2 × 200 mL). The aqueous layer was then acidified with 1 M aqueous HCl to pH 3 and extracted further with Et_2O (3 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (linear gradient 7 to 30% EtOAc/hexanes, 6 × 25 cm SiO_2), to afford 1.40 g (90%) recovered oxazolidinone and 3.50 g (94%) of the desired acid as a clear colorless oil: $[\alpha]^{23}_D$ −29.4° (*c* 1.49, CH_2Cl_2); IR (neat) 3443, 2943, 2866, 1706, 1457 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30−7.20 (m, 5H), 4.52 (d, *J* = 10.8 Hz, 1H), 4.45 (d, *J* = 10.8 Hz, 1H), 4.42 (dq, *J* = 1.7, 6.4 Hz, 1H), 4.14 (dd, *J* = 2.2, 9.4 Hz, 1H), 2.73 (dq, *J* = 2.2, 7.0 Hz, 1H), 1.53 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.06 (s on top of m, 21H), 0.86 (d, *J* = 7.0 Hz, 3H); TLC R_f = 0.18 (20% Et_2O/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 445.2750, found 445.2809.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*,5*R*,6*S*,7*R*,8*R*)-6-(benzyloxy)-1,5,7-trimethyl-3-methylene-4-oxo-8-(triisopropylsiloxy)nonyl]-5-methyl-2-phenyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (36). To a solution of 100.4 mg (0.238 mmol) of acid in 2.3 mL of benzene at ambient temperature was added 0.0415 mL (0.476 mmol) of oxalyl chloride neat via syringe. A catalytic amount (2 μL) of DMF was added, and the resultant solution was stirred for 4 h before it was azeotroped with benzene (3 × 5 mL) and placed under reduced pressure (5 Torr) for 2 h.

The pale yellow acid chloride was dissolved in 2.3 mL of benzene and treated with 10.9 mg (0.0119 mmol) of tris(dibenzylideneacetone)dipalladium, followed by 0.0128 mL (0.0714 mmol) of Hünig's base. To the resultant purple solution was added 182.8 mg (0.286 mmol) of vinylstannane. After 30 min at ambient temperature, the solution had faded to green/black, and an additional 10.9 mg of palladium was added, regenerating the purple color. After an additional 1 h, the reaction was filtered through a pad of SiO_2 with 20 mL of EtOAc, and concentrated in vacuo. The residue was purified by flash chromatography (linear gradient 7 to 10% EtOAc/hexanes, 1 × 13 cm SiO_2) to afford 178.9 mg (85%) of the desired enone as a clear colorless oil: $[\alpha]^{23}_D$ −61.0° (*c* 1.14, CH_2Cl_2); IR (solution, CH_2Cl_2) 3066, 2971, 2943, 2867, 1782, 1696, 1672 cm^{-1};^{1}H NMR (500 MHZ, $CDCl_3$) δ 7.53 (d, J = 6.8 Hz, 2H), 7.40−7.26 (m, 11H), 7.24 (d, J = 6.8 Hz, 2H), 6.09 (s, 1H), 5.81 (s, 1H), 5.56 (s, 1H), 4.72 (m, 1H), 4.37 (AB obscuring a dq, J_{AB}= 10.4 Hz, 3H), 4.24 (app t, J = 9.1 Hz, 1H), 4.20 (dd, J = 2.9, 9.1 Hz, 1H), 4.13 (m, 2H), 4.04 (dd, J = 2.6, 9.0 Hz, 1H), 3.53 (dd, J = 1.6, 9.1 Hz, 1H), 3.47 (dq, J = 2.6, 6.8 Hz, 1H), 3.26 (dd, J = 13.4, 3.2 Hz, 1H), 3.00 (q, J = 11.3 Hz, 1H), 2.78 (dd, J = 13.3, 9.5 Hz, 1H), 2.06 (m, 2H), 1.85 (m, 1H), 1.58 (m, 1H), 1.43 (d, J = 6.1 Hz, 3H), 1.23 (d, J = 6.4 Hz, 3H), 1.11 (d, J = 6.7 Hz, 3H), 1.07 (s on top of m, 21H), 0.96 (d, J = 7.0 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.81 (d, J = 6.1 Hz, 3H); TLC R_f = 0.31 (20% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 904.5160, found 904.5185.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*,4*R*,5*S*,6*R*,-7*R*,8*R*)-6-(benzyloxy)-4-hydroxy-1,5,7-trimethyl-3-methylene-8-(triisopropylsiloxy)nonyl]-5-methyl-2-phenyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (37). To a solution of 1.5 g (1.70 mmol) enone in 42.5 mL of MeOH and 42.5 mL of THF at −78 °C was added 5.06 g (13.6 mmol) $CeCl_3 \cdot 7H_2O$ and 322 mg (8.50 mmol) $NaBH_4$. The resultant mixture was stirred at that temperature for 8 h before the reaction was quenched by the addition of 75 mL of a 1 M aqueous solution of NaOH. The mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (1 × 50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (linear gradient 7.5 to 20% EtOAc/hexanes, 5 × 16 cm SiO_2), to afford 917.5 g (61%) of a major diastereomer with 85.2 mg (6%) of a conjugate reduction product (as determined by ^{1}H NMR), 303.9 mg (25%) of various oxazolidinone cleavage products (as determined by ^{1}H NMR), and 57.3 mg (4%) of a minor diastereomer. Data for the major diastereomer: $[\alpha]^{23}_D$ −53.8° (*c* 1.02, CH_2Cl_2); IR (neat) 3429, 3026, 2970, 2942, 2866, 1784, 1694, 1641 cm^{-1};^{1}H NMR (500 MHZ, $CDCl_3$) δ 7.50 (d, J = 6.8 Hz, 2H), 7.40−7.26 (m, 11H), 7.24 (d, J = 6.8 Hz, 2H), 5.56 (s, 1H), 5.09 (s, 1H), 4.93 (s, 1H), 4.73 (m, 1H), 4.68 (app s, 2H), 4.39 (dq, J = 2.0, 6.4 Hz, 1H), 4.24 (app t, J = 9.1 Hz, 1H), 4.20 (dd, J = 2.8, 9.1 Hz, 1H), 4.12 (m, 2H), 3.98 (dd, J = 4.8, 8.2 Hz, 1H), 3.94 (dd, J = <1.0, 9.0 Hz, 1H), 3.48 (dd, J = 1.8, 9.9 Hz, 1H), 3.26 (dd, J = 13.4, 3.3 Hz, 1H), 2.78 (dd, J = 13.4, 9.6 Hz, 1H), 2.76 (d, J = 16.6 Hz, 1H), 2.35 (broad s, 1H), 2.07 (m, 1H), 1.93 (m, 1H), 1.85 (m, 1H), 1.63 (m, 2H), 1.42 (d, J = 6.1 Hz, 3H), 1.21 (d, J = 6.4 Hz, 3H), 1.07 (s on top of m, 21H), 0.91 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.1 Hz, 3H), 0.85 (d, J = 6.6 Hz, 3H), 0.82 (d, J = 7.0 Hz, 3H); TLC R_f = 0.28 (20% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 906.5316, found 906.5345.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*,4*S*,5*S*,6*R*,7*R*,-8*R*)-6-(benzyloxy)-4-hydroxy-1,5,7-trimethyl-3-methylene-8-(triisopropylsiloxy)nonyl]-5-methyl-2-phenyl-*m*-dioxan-4-yl]-propionyl]-2-oxazolidinone. Data for the minor diastereomer: $[\alpha]^{23}_D$ −37.5° (*c* 0.385, CH_2Cl_2); IR (solution, CH_2Cl_2) 3686, 3064, 2941, 2867, 1782, 1695 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 6.8 Hz, 2H), 7.40−7.26 (m, 11H), 7.23 (d, J = 6.8 Hz, 2H), 5.53 (s, 1H), 5.19 (s, 1H), 4.95 (s, 1H), 4.78 (d, J = 10.1 Hz, 1H), 4.73 (m, 1H), 4.60 (d, J = 10.1 Hz, 1H), 4.31−4.19 (m, 4H), 4.11 (m, 2H), 3.72 (dd, J = 1.7, 8.5 Hz, 1H), 3.45 (dd, J = 1.6, 9.7 Hz, 1H), 3.32 (s, 1H), 3.26 (dd, J = 13.4, 3.2 Hz, 1H), 2.77 (dd, J = 13.3, 9.6 Hz, 1H), 2.65 (d, J = 13.2 Hz, 1H), 1.92−1.82 (m, 3H), 1.72 (m, 2H), 1.41 (d, J = 6.1 Hz, 3H), 1.16 (d, J = 6.3 Hz, 3H), 1.04 (s on top of m, 21H), 0.90 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.9 Hz, 3H); TLC R_f = 0.16 (20% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 906.5316, found 906.5348.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*S*,9*R*,10*R*,11*S*,12*R*,13*R*)-3,5-[(*S*)-(Benzylidene)dioxy]-11-(benzyloxy)-9-(*tert*-butyldimethylsiloxy)-8,8-(epoxymethano)-2,4,6,10,12,13-hexamethyltetradecanolide (39). To a solution of 17.0 mg (0.0244 mmol) of azeotropically dried hydroxy acid in 0.5 mL of benzene at ambient temperature was added 0.131 mL (0.731 mmol) of Hünig's base and 0.0761 mL (0.487 mmol) of 2,4,6-trichlorobenzoyl chloride. The solution was stirred at room temperature for 12 h before it was diluted with an additional 5.6 mL of benzene and treated with 119.0 mg (0.974 mmol) of *N*,*N*-(dimethylamino)pyridine. After 12 h at ambient temperature the white mixture was quenched by the addition of 5 mL of saturated aqueous NH_4Cl solution. The mixture was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine (1 × 5 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Analysis of the unpurified mixture by ^{1}H NMR revealed a 2.5:1 ratio of compounds later determined by LRMS to correspond to the monomer and diolide [TLC R_f (dimer) = 0.66 (30% EtOAc/hexanes)] respectively. The monomer was purified by flash chromatography (7% EtOAc/hexanes, 2 × 12 cm SiO_2) to afford 7.6 mg (46%) of the desired macrocycle as a clear colorless oil: $[\alpha]^{23}_D$ −4.8° (*c* 0.507, CH_2Cl_2); IR (solution, CH_2Cl_2) 3071, 2935, 2861, 1724, 1457 cm^{-1}; ^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.60−7.30 (m, 10H), 5.63 (q, J = 6.5 Hz, 1H), 5.59 (s, 1H), 5.02 (d, J = 10.0 Hz, 1H), 4.17 (d, J = 10.0 Hz, 1H), 4.02 (d, J = 10.2 Hz, 1H), 3.92 (d, J = 3.3 Hz, 1H), 3.68 (dd, J = 1.0, 11.0 Hz, 1H), 3.31 (d, J = 9.6 Hz, 1H), 3.18 (d, J = 4.5 Hz, 1H), 2.89 (d, J = 4.6 Hz, 1H), 2.86 (dq, J = 6.6, 11.0 Hz, 1H), 2.21 (m, 1H), 2.14 (m, 1H), 2.02 (dd, J = 11.3, 15.7 Hz, 1H), 1.95 (m, 1H, C_4−*H*), 1.77 (d, J = 15.7 Hz, 1H), 1.78 (m, 1H), 1.24 (d, J = 6.6 Hz, 3H), 1.23 (d, J = 6.5 Hz, 3H), 1.20 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 7.4 Hz, 3H), 1.09 (d, J = 7.0 Hz, 3H), 0.99 (d, J = 7.4 Hz, 3H), 0.86 (s, 9H), 0.109 (s, 3H), 0.107 (s, 3H); TLC R_f = 0.81 (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 703.4006, found 703.3997.

(4*R*)-4-Benzyl-3-[(2*R*,3*S*,4*S*,5*R*)-3-(triethylsiloxy)-5-(triisopropylsiloxy)-2,4-dimethyl-1-oxohexyl]-2-oxazolidinone (40). To a solution of 1.835 g (3.74 mmol) alcohol in 75 mL of CH_2Cl_2 at room temperature was added 0.653 mL (5.61 mmol) of 2,6-lutidine, followed by 0.930 mL (4.11 mmol) of TESOTf. The resultant clear colorless solution was stirred for 40 min before the addition of 50 mL of a saturated solution of aqueous $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) The combined organics were washed with 1 *N* $NaHSO_4$ (1 × 20 mL), H_2O (1 × 20

mL), and brine (1 × 20 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The major isomer was purified by flash chromatography (10% EtOAc/hexanes, 5 × 15 cm SiO_2) to yield 2.28 g (100%) of a clear colorless oil: $[\alpha]^{23}_D$ −48.7° (*c* 1.31, CH_2Cl_2); IR (neat) 3065, 3029, 2945, 2868, 1786, 1700 cm^{-1};^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.40−7.19 (m, 5H), 4.59 (m, 1H), 4.17 (dd, *J* = 2.0, 9.0 Hz, 1H), 4.16 (dd, *J* = 6.0, 2.5 Hz, 1H), 4.12 (app t, *J* = 7.4 Hz, 1H), 4.00 (app quint, *J* = 6.8 Hz, 1H), 3.82 (app quint, *J* = 6.1 Hz, 1H), 3.26 (dd, *J* = 13.3, 3.1 Hz, 1H), 2.75 (dd, *J* = 13.3, 9.7 Hz, 1H), 1.54 (m, 1H), 1.25 (d, *J* = 7.1 Hz, 3H), 1.21 (d, *J* = 6.9 Hz, 3H), 1.05 (s on top of m, 21H), 1.00 (d, *J* = 7.2 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.63 (q, *J* = 8.2 Hz, 6H); TLC R_f = 0.76 (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 628.3830, found 628.3802.

(2*R*,3*S*,4*S*,5*R*)-3-(triethylsiloxy)-5-(triisopropylsiloxy)-2,4-dimethylhexanoic Acid (40a). To a solution of 220.4 mg (0.364 mmol) of imide in 11.3 mL of THF at 0 °C was added 0.330 mL (2.91 mmol) of a 30% aqueous solution of H_2O_2 followed by 3.64 mL (0.728 mmol) of a 0.2 M aqueous solution of LiOH. The resultant clear colorless solution was stirred at 0 °C for 2 d before it was quenched by the addition of 10 mL of a 1.5 M aqueous solution of Na_2SO_3. The mixture was stirred vigorously at 0 °C. After 30 min, the mixture was extracted by CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (10% EtOAc/hexanes, 3 × 13.5 cm SiO_2), to afford 63.2 mg (98%) of recovered oxazolidinone and 147.6 mg (91%) of the desired acid as a clear colorless oil: $[\alpha]^{23}_D$ −8.91° (*c* 1.10, CH_2Cl_2); IR (neat) 3077, 2946, 2868, 2728, 2636, 1708 cm^{-1};^{1}H NMR (400 MHZ, $CDCl_3$) δ 4.23 (dd, *J* = 3.8, 5.8 Hz, 1H), 4.00 (app quint, *J* = 6.1 Hz, 1H), 2.70 (dq, *J* = 3.8, 7.0 Hz, 1H), 1.58 (m, 1H), 1.24 (d, *J* = 6.2 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.07 (s on top of m, 21H), 0.95 (d, *J* = 7.2 Hz, 3H), 0.94 (t, *J* = 7.8 Hz, 9H), 0.61 (q, *J* = 7.8 Hz, 6H); TLC R_f = 0.69 (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 469.3145, found 469.3144.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*,5*R*,6*S*,7*S*,8*R*)-6-(triethylsiloxy)-1,5,7-trimethyl-3-methylene-4-oxo-8-(triisopropylsiloxy)nonyl]-5-methyl-2-phenyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (42). To a solution of 140.0 mg (0.326 mmol) acid in 6.5 mL of benzene at ambient temperature was added 0.0710 mL (0.814 mmol) of oxalyl chloride neat via syringe. A catalytic amount (2 μL) of DMF was added, and the resultant solution was stirred for 4 h before it was azeotroped with benzene (3 × 10 mL) and placed under reduced pressure (5 Torr) for 2 h.

The pale yellow acid chloride was dissolved in 5.0 mL of benzene and treated with 9.4 mg (0.0103 mmol) of tris(dibenzylideneacetone)dipalladium, followed by 0.0110 mL (0.0614 mmol) of Hünig's base. To the resultant purple solution was added 130.9 mg (0.205 mmol) of vinylstannane in 1.5 mL of benzene (1 × 1 mL rinse) via cannula. After 30 min at ambient temperature, the solution had faded to green/black, and an additional 9.4 mg of palladium was added to regenerate the purple color. After an additional 10 h, the reaction was filtered through a pad of SiO_2 with 20 mL of EtOAc, and concentrated in vacuo. The residue was purified by flash chromatography (linear gradient 50% CH_2Cl_2/hexanes to 68% CH_2Cl_2/2% EtOAc/30% hexanes, 3 × 11 cm SiO_2) to afford 9.5 mg (17%) of the lactone derived from the excess carboxylic acid and 162.5 mg (88%) of the desired enone as a clear pale yellow oil: $[\alpha]^{23}_D$ −45.4° (*c* 1.03, CH_2Cl_2); IR (neat) 3036, 2944, 2868, 1784, 1694, 1677 cm^{-1}; ^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.53 (d, *J* = 6.8 Hz, 2H), 7.40−7.26 (m, 6H), 7.23 (d, *J* = 6.8 Hz, 2H), 6.10 (s, 1H), 5.74 (s, 1H), 5.56 (s, 1H), 4.72 (m, 1H), 4.24 (app t, *J* = 9.1 Hz, 1H), 4.19 (dd, *J* = 3.0, 9.1 Hz, 1H), 4.16 (app t, *J* = 5.2 Hz, 1H), 4.12 (m, 2H), 3.68 (app quint, *J* = 6.2 Hz, 1H), 3.50 (dd, *J* = 1.5, 9.0 Hz, 1H), 3.44 (app quint, *J* = 6.5 Hz, 1H), 3.26 (dd, *J* = 13.3, 3.3 Hz, 1H), 3.00 (q, *J* = 11.1 Hz, 1H), 2.77 (dd, *J* = 13.3, 9.5 Hz, 1H), 1.94 (m, 2H), 1.85 (q, *J* = 7.0 Hz, 1H), 1.54 (m, 1H), 1.43 (d, *J* = 6.0 Hz, 3H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.05 (d, *J* = 7.2 Hz, 3H), 1.03 (s on top of m, 21H), 0.99 (d, *J* = 7.0 Hz, 3H), 0.95 (t, *J* = 8.0 Hz, 9H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.75 (d, *J* = 6.1 Hz, 3H), 0.61 (q, *J* = 7.9 Hz, 6H); TLC R_f = 0.29 (67% CH_2Cl_2/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 928.5555 found 928.5542.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*,5*R*,6*S*,7*R*,8*R*)-6-hydroxy-1,5,7-trimethyl-3-methylene-4-oxo-8-(triisopropylsiloxy)nonyl]-5-methyl-2-phenyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (42a). To a solution of 162.5 mg (0.180 mmol) in 5 mL of THF at 0 °C in a Nalgene bottle was added approximately 4 mL of an HF·pyridine stock solution (2 mL of HF·pyridine, 4 mL of pyridine, and 16 mL of THF). After 2.5 h, the reaction was quenched by the dropwise addition of 50 mL of saturated aqueous $NaHCO_3$ solution, and the resultant mixture was stirred at 0 °C for 30 min. The mixture was then partitioned between 10 mL of CH_2Cl_2 and 10 mL of H_2O. The aqueous layer was separated and extracted with CH_2Cl_2 (5 × 10 mL). The combined organic layers were washed with a 1 M aqueous solution of $NaHSO_4$, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (linear gradient 10 to 20% EtOAc/hexanes, 2 × 13.5 cm SiO_2) to afford 135.1 mg (95%) of a clear colorless oil: $[\alpha]^{23}_D$ −45.2° (*c* 0.782, CH_2Cl_2); IR (neat) 3462, 3036, 2968, 2941, 2867, 1784, 1693, 1662 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 6.8 Hz, 2H), 7.40−7.20 (m, 8H), 5.97 (s, 1H), 5.71 (s, 1H), 5.56 (s, 1H), 4.72 (m, 1H), 4.26 (dq, *J* = 2.3, 6.4 Hz, 1H), 4.24 (app t, *J* = 10.1 Hz, 1H), 4.19 (dd, *J* = 2.9, 9.1 Hz, 1H), 4.12 (m, 2H), 4.03 (dd, *J* = 2.2, 11.2 Hz, 1H), 3.51 (dd, *J* = 1.8, 9.9 Hz, 1H), 3.28 (dq, *J* = 2.4, 7.1 Hz, 1H), 3.25 (dd, *J* = 13.3, 3.1 Hz, 1H), 2.87 (dd, *J* = 3.3, 14.1 Hz, 1H), 2.77 (dd, *J* = 13.3, 9.5 Hz, 1H), 2.18 (dd, *J* = 9.1, 14.1 Hz, 1H), 1.91 (m, 1H), 1.82 (q, *J* = 7.0 Hz, 1H), 1.71 (m, 1H), 1.42 (d, *J* = 6.1 Hz, 3H), 1.19 (d, *J* = 6.4 Hz, 3H), 1.08 (d, *J* = 6.9 Hz, 3H), 1.05 (s on top of m, 21H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.77 (d, *J* = 6.8 Hz, 3H), 0.765 (d, *J* = 7.0 Hz, 3H); TLC R_f = 0.50 (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 814.4690 found 814.4689.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*,4*S*,5*R*,6*R*,-7*R*,8*R*)-4,6-dihydroxy-1,5,7-trimethyl-3-methylene-8-(triisopropylsiloxy)nonyl]-5-methyl-2-phenyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (43). To a clear yellow solution of purified aldol adduct (302.0 g, 0.382 mmol) in 19.1 mL of CH_2Cl_2 at −50 °C was added a solution of $Zn(BH_4)_2$ in Et_2O (20.4 mL, 0.15 M solution). The resultant clear solution was stirred for 15.5 h at −50 °C before the reaction was warmed to 0 °C and maintained at that temperature for 1 h. The reaction was then treated with 20 mL of a saturated aqueous solution of NH_4Cl at 0 °C. The mixture was stirred vigorously as it was warmed to ambient temperature. After 10 min at ambient temperature, the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resultant clear colorless oil was azeotroped with MeOH (3 × 100 mL). Analysis of the unpurified material by HPLC (Zorbax, 15% EtOAc/hexanes, flow rate 2.0 mL/min, 254 nm) revealed a >99:1 ratio of

diastereomers. The product was purified by flash chromatography (linear gradient 10 to 20% EtOAc/hexanes, 3 × 11 cm SiO_2), to afford 260.5 mg (86%) of a clear colorless oil: $[\alpha]^{23}_D$ −36.5° (*c* 1.01, CH_2Cl_2); IR (neat) 3423, 2942, 2967, 1785, 1694 cm^{-1};^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.50−7.20 (m, 10H), 5.53 (s, 1H), 5.25 (s, 1H), 5.15 (s, 1H), 4.94 (s, 1H), 4.73 (m, 1H), 4.34 (s, 1H), 4.32 (s, 1H), 4.24 (app t, J = 9.1 Hz, 1H), 4.19 (dd, J = 2.8, 9.1 Hz, 1H), 4.10 (m, 2H), 4.02 (dq, J = 3.2, 6.4 Hz, 1H), 3.91 (d, J = 10.2 Hz, 1H), 3.51 (dd, J = 1.7, 9.7 Hz, 1H), 3.25 (dd, J = 3.3, 13.3 Hz, 1H), 2.77 (dd, J = 13.3, 9.5 Hz, 1H), 2.66 (d, J = 13.5 Hz, 1H), 1.96 (m, 1H), 1.84 (q, J = 7.0 Hz, 1H), 1.81 (m, 1H), 1.66 (m, 2H), 1.41 (d, J = 6.1 Hz, 3H), 1.23 (d, J = 6.4 Hz, 3H), 1.07 (s on top of m, 21H), 0.89 (d, J = 6.9 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.80 (d, J = 7.0 Hz, 3H), 0.51 (d, J = 7.1 Hz, 3H); TLC R_f = 0.43 (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 816.4847 found 816.4856.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*)-2-[(2*R*)-2-[(1*S*,2*R*,3*R*,4*R*,5*R*)-1,3-dihydroxy-2,4-dimethyl-5-(triisopropylsiloxy)hexyl]oxiranyl]-1-methylethyl]-5-methyl-2-phenyl-*m*-dioxan-4-yl)propionyl]-2-oxazolidinone (44). To a solution of 114.0 mg (0.144 mmol) diol in 14 mL of benzene at ambient temperature was added ∼0.100 mL (0.550 mmol) of a 5.5 M solution of *tert*-butyl hydroperoxide in decane followed by 2.0 mg (0.00719) of $VO(acac)_2$. The wine red solution was stirred for 45 min before the reaction was quenched by the addition of 15 mL of a 1 M aqueous solution of Na_2SO_3. The mixture was extracted with Et_2O (2 × 10 mL). The combined organic layers were then washed with brine (1 × 10 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (30% EtOAc/hexanes, 2 × 9 cm Et_3N-doped SiO_2) to afford 106.3 mg (91%) of a clear colorless oil: $[\alpha]^{23}_D$ −27.2° (*c* 1.16, CH_2Cl_2); IR (neat) 3434, 3036, 2941, 2886, 1785, 1695 cm^{-1};^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.50−7.20 (m, 10H), 5.51 (s, 1H), 4.87 (s, 1H), 4.73 (m, 1H), 4.25 (app t, J = 9.1 Hz, 1H), 4.20 (dd, J = 2.8, 9.2 Hz, 1H), 4.18 (s, 1H), 4.09 (m, 2H), 4.05 (dq, J = 2.9, 6.6 Hz, 1H), 3.85 (d, J = 10.1 Hz, 1H), 3.70 (s, 1H), 3.36 (dd, J = 1.7, 9.9 Hz, 1H), 3.25 (dd, J = 3.3, 13.3 Hz, 1H), 3.06 (d, J = 4.5 Hz, 1H), 2.77 (dd, J = 13.3, 9.5 Hz, 1H), 2.68 (d, J = 1.3, 14.7 Hz, 1H), 2.41 (d, J = 5.5 Hz, 1H), 1.90−1.75 (m, 4H), 1.40 (d, J = 6.1 Hz, 3H), 1.19 (d, J = 6.4 Hz, 3H), 1.05 (s on top of m, 21H), 1.01 (d, J = 6.6 Hz, 3H), 1.94 (m, 1H), 0.87 (d, J = 6.7 Hz, 3H), 0.85 (d, J = 6.8 Hz, 3H), 0.40 (d, J = 7.0 Hz, 3H); TLC R_f = 0.19 (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 832.4796 found 832.4796.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*)-2-[(2*R*)-2-[(1*S*,2*R*,3*S*,4*R*,5*R*)-1-(*tert*-butyldimethylsiloxy)-3-hydroxy-2,4-dimethyl-5-(triisopropylsiloxy)hexyl]oxiranyl]-1-methylethyl]-5-methyl-2-phenyl-*m*-dioxan-4-yl)propionyl]-2-oxazolidinone (46). To a solution of 182.0 mg (0.225 mmol) of epoxy diol in 22.5 mL of CH_2Cl_2 at −78 °C was added 0.210 mL (1.80 mmol) of 2,6-lutidine, followed by 0.258 mL (1.12 mmol) of TBSOTf. The resultant clear colorless solution was stirred at −78 °C for 19 h. The reaction was quenched by the addition of 4 mL of a saturated solution of aqueous $NaHCO_3$ and warmed to ambient temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with 1 *N* $NaHSO_4$ (1 × 10 mL) and brine (1 × 10 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (10% EtOAc/hexanes with 1 mL of Et_3N/500 mL eluant, 3 × 12 cm SiO_2) to yield 172.1 g (83%) of a clear colorless oil: $[\alpha]^{23}_D$ −48.1° (*c* 1.01 CH_2Cl_2); IR (neat) 3472, 3036, 2940, 2865, 1784, 1695 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.20 (m, 10H), 5.50 (s, 1H), 4.72 (m, 1H), 4.24 (app t, J = 9.1 Hz, 1H), 4.20 (dd, J = 2.9, 9.1 Hz, 1H), 4.19 (m, 1H), 4.09 (m, 2H), 3.85 (d, J = 9.9 Hz, 1H), 3.67 (s, 1H), 3.63 (d, J = 5.6 Hz, 1H), 3.36 (dd, J = 1.8, 9.8 Hz, 1H), 3.25 (dd, J = 3.3, 13.3 Hz, 1H), 2.77 (dd, J = 13.3, 9.6 Hz, 1H), 2.69 (d, J = 5.1 Hz, 1H), 2.50 (m, 2H), 1.90 (m, 1H), 1.83 (q, J = 7.1 Hz, 1H), 1.72 (m, 1H), 1.60 (m, 1H), 1.40 (d, J = 6.2 Hz, 3H), 1.26 (m, 1H), 1.11 (d, J = 6.4 Hz, 3H), 1.05 (s on top of m, 21H), 0.95 (d, J = 6.7 Hz, 3H), 0.89 (s, 9H), 0.88 (d, J = 6.7 Hz, 3H), 0.86 (d, J = 6.6 Hz, 3H), 0.56 (d, J = 7.0 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H); TLC R_f = 0.58 (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 946.5661 found 946.5696.

(4*R*)-4-Benzyl-3-[(2*R*)-2-[(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*)-2-[(2*S*,3*S*,-4*R*,5*S*)-3-(*tert*-butyldimethylsiloxy)tetrahydro-2-(hydroxymethyl)-4-methyl-5-[(1*R*,2*R*)-1-methyl-2-(triisopropylsiloxy)propyl]-2-furyl]-1-methylethyl]-5-methyl-2-phenyl-*m*-dioxan-4-yl]propionyl]-2-oxazolidinone (46). Data for the rearranged tetrahydrofuran compound: $[\alpha]^{23}_D$ −40.0° (*c* 0.600, CH_2Cl_2); IR (neat) 3539, 3032, 2939, 2865, 1785, 1694 cm^{-1};^{1}H NMR (500 MHZ, $CDCl_3$) δ 7.50−7.20 (m, 10H), 5.49 (s, 1H), 4.72 (m, 1H), 4.36 (dq, J = 1.1, 6.4 Hz, 1H), 4.24 (app t, J = 9.1 Hz, 1H), 4.20 (dd, J = 2.8, 9.1 Hz, 1H), 4.10 (m, 1H), 4.07 (dd, J = 1.3, 10.0 Hz, 1H), 4.02 (dd, J = 3.1, 10.4 Hz, 1H), 3.92 (s, 1H), 3.76 (d, J = 13.1 Hz, 1H), 3.39 (m, 2H), 3.25 (dd, J = 3.2, 13.4 Hz, 1H), 2.76 (dd, J = 13.4, 9.6 Hz, 1H), 1.84 (m, 2H), 1.68 (m, 1H), 1.60 (m, 2H), 1.51 (dd, J = 7.3, 13.4 Hz, 1H), 1.37 (d, J = 6.1 Hz, 3H), 1.14 (d, J = 6.4 Hz, 3H), 1.05 (s on top of m, 21H), 0.95 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.9 Hz, 3H), 0.83 (s, 9H), 0.72 (d, J = 6.7 Hz, 3H), 0.51 (d, J = 7.4 Hz, 3H), 0.02 (s, 3H), −0.05 (s, 3H); TLC R_f = 0.64 (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for [M + Na]$^+$ 946.5661 found 946.5669.

(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*)-2-[(2*R*)-2-[(1*S*,2*R*,3*S*,4*R*,5*R*)-1-(*tert*-Butyldimethylsiloxy)-3-hydroxy-2,4-dimethyl-5-(triisopropylsiloxy)hexyl]oxiranyl]-1-methylethyl]-4-[(1*R*)-1-carboxyeth-1-yl]-5-methyl-2-phenyl-*m*-dioxane (47). To a solution of 172.1 mg (0.186 mmol) of imide in 5.7 mL of THF at 0 °C was added 0.169 mL (1.49 mmol) of a 30% aqueous solution of H_2O_2 followed by 1.86 mL (0.372 mmol) of a 0.2 M aqueous solution of LiOH. The resultant clear colorless solution was stirred at 0 °C for 36 h before an additional aliquot of H_2O_2 solution was added. After a total of 60 h, the reaction was quenched by the addition of 5 mL of a 1.5 M aqueous solution of Na_2SO_3. The mixture was stirred vigorously at 0 °C. After 30 min, the mixture was extracted by CH_2Cl_2 (7 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (linear gradient of 40% EtOAc/hexanes with 1 mL of Et_3N/500 mL eluant to 50% EtOAc/hexanes with 5 drops of Et_3N/100 mL eluant, to 5−10% MeOH/CH_2Cl_2, 2 × 14.5 cm SiO_2) to yield 28.7 mg (87%) of recovered oxazolidinone and 159.2 g (93%) of a 1.5:1 Et_3N to acid complex as a clear colorless oil. In an analogous procedure, 128.8 mg (0.140 mmoL) of the starting imide was cleaved to the carboxylic acid and purified without Et_3N to afford 98.1 mg (92%) of the desired acid as a clear colorless oil for characterization purposes: $[\alpha]^{23}_D$ −12.2° (*c* 1.02 CH_2Cl_2); IR (neat) 3477, 3036, 2940, 2866, 1738, 1709 cm^{-1};^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.50−7.30 (m, 5H), 5.46 (s, 1H), 4.19 (dq, J = 1.4, 6.4, 1H), 3.87 (d, J = 9.9 Hz, 1H), 3.83 (d, J = 11.1 Hz, 1H), 3.63 (d, J = 5.3 Hz, 1H), 3.32 (d, J = 9.8 Hz, 1H), 2.80 (dq, J = 6.9, 9.9 Hz, 1H), 2.69 (d, J = 5.0 Hz, 1H), 2.51 (d, J =

5.0 Hz, 1H), 2.48 (d, $J = 14.9$ Hz, 1H), 1.90 (m, 1H), 1.82 (q, $J = 6.8$ Hz, 1H). 1.74 (m, 1H), 1.61 (m, 1H), 1.35 (d, $J = 6.8$ Hz, 3H), 1.26 (m, 1H), 1.11 (d, $J = 6.4$ Hz, 3H), 1.05 (s on top of m, 21H), 0.97 (d, $J = 6.9$ Hz, 3H), 0.94 (d, $J = 6.6$ Hz, 3H), 0.89 (s, 9H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.56 (d, $J = 7.0$ Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H); TLC $R_f = 0.25$ (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 787.4976 found 787.4979.

(2*S*,4*S*,5*R*,6*S*)-6-[(1*S*)-2-[(2*R*)-2-[(1*S*,2*R*,3*S*,4*S*,5*R*)-1-(*tert*-Butyldimethylsiloxy)-3,5-dihydroxy-2,4-dimethylhexyl]oxiranyl]-1-methylethyl]-4-[(1*R*)-1-carboxyeth-1-yl]-5-methyl-2-phenyl-*m*-dioxane (48). To a solution of 58.1 mg (0.0634 mmoL) of a 1.5:1 Et_3N to acid complex in 3.2 mL of THF was added 0.0855 mL (6.35 mmol) of Et_3N, followed by ~500 mg of Et_3N·HF (excess) (which had been prepared from HF·pyridine complex and Et_3N, pyridine, and unreacted Et_3N pumped off in vacuo, and stored as a white crystalline solid under argon). The slightly opalescent mixture was stirred at ambient temperature for 9 d with additional Et_3N·HF added at 14 h and day 3 before the reaction was quenched at 0 °C by the dropwise addition of 5 mL of a saturated aqueous solution of $NaHCO_3$. The residue was purifed by prep plate chromatography (1 mm, 5% MeOH/CH_2Cl_2 with 2 mL Et_3N/200 mL eluant) to afford 2.3 mg (4%) starting material and 35.5 mg (79%, 83% based on recovered starting material) of a 1:1 Et_3N to desired dihydroxy acid complex as a clear colorless oil. In an analogous procedure, 101.1 mg (0.110 mmol) of Et_3N-free starting acid was desilylated in a similar manner and purified without the presence of Et_3N to afford 17.4 mg (17.2%) recovered starting material and 37.2 mg (56%, 70% based on recovered starting material) of Et_3N-free dihydroxy acid as a clear colorless oil: $[\alpha]^{23}_D$ +2.7° (*c* 0.811 $CHCl_3$); IR (neat) 3446, 3068, 2974, 2933, 2862, 2574, 1782 cm^{-1};^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.44−7.33 (m, 5H), 5.49 (s, 1H), 3.86−3.70 (m, 5H), 3.33 (dd, $J = 1.7$, 9.8 Hz, 1H), 2.81 (dq, $J = 6.9$, 10.1 Hz, 1H), 2.73 (d, $J = 5.0$ Hz, 1H), 2.58 (d, $J = 14.7$ Hz, 1H), 2.51 (d, $J = 4.7$ Hz, 1H), 1.90 (m, 1H), 1.82 (m, 2H), 1.74 (m, 1H), 1.37 (d, $J = 6.8$ Hz, 3H), 1.15 (m, 1H), 1.09 (d, $J = 6.5$ Hz, 3H), 0.98 (d, $J = 6.9$ Hz, 3H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.91 (d, $J = 6.9$ Hz, 3H), 0.89 (s, 9H), 0.54 (d, $J = 7.0$ Hz, 3H), 0.13 (s, 3H), 0.12 (s, 3H); TLC $R_f = 0.35$ (10% MeOH/CH_2Cl_2). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 631.3642 found 631.3657.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,9*S*,10*R*,11*S*,12*S*,13*R*)-3,5-[(*S*)-(Benzylidene)dioxy]-9-(*tert*-butyldimethylsiloxy)-8,8-(epoxymethano)-11-hydroxy-2,4,6,10,12,13-hexamethyltetradecanolide (51). To a solution of 30.0 mg (0.0493 mmol) of Et_3N−free dihydroxy acid in 0.5 mL of benzene at ambient temperature were added 0.265 mL (1.48 mmol) of Hünig's base and 0.154 mL (0.987 mmol) 2,4,6-trichlorobenzoyl chloride. The resultant solution was stirred at ambient temperature for 8 h before it was diluted by the addition of 50 mL of benzene and treated with 240.9 mg (1.97 mmol) *N*,*N*-(dimethylamino)pyridine. After 24 h, the resultant white mixture was quenched by the addition of 30 mL of a saturated aqueous solution of NH_4Cl. The mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (15% EtOAc/hexanes after loading in CH_2Cl_2, 1 × 15 cm SiO_2) to afford 29.2 mg (100%) of a clear colorless oil: $[\alpha]^{23}_D$ +3.7° (*c* 0.310 CH_2Cl_2); IR (neat) 3552, 3036, 2934, 2887, 1727 cm^{-1};^{1}H NMR (400 MHZ, $CDCl_3$) δ 7.52−7.33 (m, 5H), 5.77 (dq, $J = 1.2$, 6.6 Hz, 1H), 5.55 (s, 1H), 3.92 (dd, $J = 1.1$, 7.0 Hz, 1H), 3.83 (dd, $J = 4.0$, 10.0 Hz, 1H), 3.70 (dd, $J = 0.9$, 11.0 Hz, 1H), 2.97 (d, $J = 9.7$ Hz, 1H), 2.94 (d, $J = 4.0$ Hz, 1H), 2.84 (dq, $J = 6.6$, 11.0 Hz, 1H), 2.47 (d, $J = 4.0$ Hz, 1H), 2.35 (d, $J = 5.8$ Hz, 1H), 2.18 (dd, $J = 2.0$, 15.5 Hz, 1H), 2.13 (m, 1H), 2.09 (m, 1H), 1.99 (dd, $J = 12.1$, 15.5 Hz, 1H), 1.94 (m, 1H), 1.60 (m, 1H), 1.26 (d, $J = 6.6$ Hz, 3H), 1.22 (d, $J = 6.6$ Hz, 3H), 1.14 (d, $J = 6.7$ Hz, 3H), 1.11 (d, $J = 7.0$ Hz, 3H), 0.94 (d, $J = 7.1$ Hz, 3H), 0.92 (d, $J = 5.3$ Hz, 3H), 0.91 (s, 9H), 0.08 (s, 3H), 0.04 (s, 3H); TLC $R_f = 0.49$ (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 613.3537 found 613.3543.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,9*S*,10*R*,11*S*,12*S*,13*R*)-3,5-[(*S*)-(Benzylidene)dioxy]-8,8-(epoxymethano)-9,11-dihydroxy-2,4,6,-10,12,13-hexamethyltetradecanolide (52). To a solution of 4.6 mg (0.0078 mmol) in 0.250 mL of THF at ambient temperature in a polyethylene tube was added approximately 0.250 mL of an HF·pyridine stock solution (2 mL of HF·pyridine, 4 mL of pyridine, and 16 mL of THF). After 2.5 d, the reaction was cooled to 0 °C and quenched by the dropwise addition of 5 mL of saturated aqueous $NaHCO_3$ solution. The mixture was then partitioned between 5 mL of CH_2Cl_2 and 5 mL of H_2O. The aqueous layer was separated and extracted with CH_2Cl_2 (5 × 5 mL). The combined organic layers were washed with a 1 M aqueous solution of $NaHSO_4$, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (50% EtOAc/hexanes with 20 drops of pyridine/100 mL of eluant, 0.75 × 9.5 cm SiO_2) to afford 3.7 mg (100%) of a clear colorless oil: $[\alpha]^{23}_D$ +5.4° (*c* 0.245 CH_2Cl_2); IR (neat) 3479, 3036, 2975, 2938, 2882, 1728 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50−7.30 (m, 5H), 5.77 (dq, $J = 1.2$, 6.6 Hz, 1H), 5.56 (s, 1H), 3.97 (d, $J = 7.1$ Hz, 1H), 3.84 (dd, $J = 3.6$, 10.2 Hz, 1H), 3.71 (dd, $J = 1.1$, 10.9 Hz, 1H), 3.01 (d, $J = 10.2$ Hz, 1H), 2.98 (d, $J = 4.0$ Hz, 1H), 2.85 (dq, $J = 6.6$, 11.0 Hz, 1H, 2.53 (d, $J = 4.0$ Hz, 1H), 2.38 (d, $J = 5.5$ Hz, 1H), 2.21 (dd, $J = 2.3$, 15.5 Hz, 1H), 2.11 (m, 2H), 1.97 (dd on top of m, $J = 11.9$, 15.5 Hz, 2H), 1.63 (m, 1H), 1.27 (d, $J = 6.6$ Hz, 3H), 1.22 (d, $J = 6.6$ Hz, 3H), 1.15 (d, $J = 6.7$ Hz, 3H), 1.11 (d, $J = 7.1$ Hz, 3H), 1.01 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 7.1$ Hz, 3H); TLC $R_f =$ 0.06 (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 499.2672 found 499.2659.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,10*R*,11*S*,12*S*,13*R*)-3,5-[(*S*)-(Benzylidene)dioxy]-8,8-(epoxymethano)-11-hydroxy-2,4,6,10,12,13-hexamethyl-9-oxotetradecanolide (52a). To a solution of 4.9 mg (0.0103 mmol) dihydroxylactone in 0.5 mL of CH_2Cl_2 and 0.5 mL of DMF at ambient temperature was added (0.0143 mL, 0.103 mmol) triethylamine and via cannula a solution of 13.1 mg (0.0824 mmol) of SO_3·pyridine in 0.5 mL of DMF. After 1 h, the reaction was treated with equal allotments of Et_3N and oxidizing agent. Again at 2 h, a third allotment was added and the reaction stirred for 1 h (total 3 h). The reaction was quenched by the addition of 5 mL of a saturated aqueous solution of $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with a 1 M aqueous solution of $NaHSO_4$ (1 × 3 mL), brine (1 × 3 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (20% EtOAc/hexanes, 0.75 × 9 cm SiO_2) to afford 4.1 mg (84%) of a clear colorless oil: $[\alpha]^{23}_D$ −49.1° (*c* 0.205 CH_2Cl_2); IR (neat) 3520, 3067, 2976, 2941, 1727, 1715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53−7.32 (m, 5H), 5.77 (dq, $J =$ 1.1, 6.6 Hz, 1H), 5.58 (s, 1H), 4.39 (dd, $J = 3.6$, 10.3 Hz, 1H), 4.04 (dd, $J = 1.3$, 6.9 Hz, 1H), 3.77 (dd, $J = 1.1$, 10.9 Hz, 1H), 3.13 (d, $J = 4.2$ Hz, 1H), 3.06 (dq, $J = 1.9$, 6.7 Hz, 1H),

3.01 (d, $J = 4.2$ Hz, 1H), 2.89 (dq, $J = 6.6$, 10.9 Hz, 1H), 2.41 (d, $J = 5.4$ Hz, 1H), 2.32 (dd, $J = 12.2$, 15.0 Hz, 1H), 2.21 (m, 2H), 2.09 (dd, $J = 1.9$, 15.0 Hz, 1H), 1.66 (m, 1H), 1.30 (d, $J = 6.6$ Hz, 3H), 1.25 (d, $J = 6.6$ Hz, 3H), 1.21 (d, $J = 6.7$ Hz, 3H), 1.13 (d, $J = 7.0$ Hz, 3H), 1.06 (d, $J = 6.6$ Hz, 3H), 1.03 (d, $J = 7.1$ Hz, 3H); TLC $R_f = 0.92$ (30% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 497.2515 found 497.2510.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,10*R*,11*S*,12*S*,13*R*)-8,8-(Epoxymethano)-3,5,11-trihydroxy-2,4,6,10,12,13-hexamethyl-9-oxotetradecanolide, Oleandolide (2). To a solution of 3.1 mg (0.00654 mmol) of acetal in 1 mL of 1,4-dioxane was added 3.1 mg of 20% $Pd(OH)_2/C$. The mixture was stirred under an atmosphere of H_2 (balloon pressure) for 1 h before the reaction was filtered through a plug of Celite with 5 mL of EtOAc. Concentration in vacuo afforded 2.6 mg (100%) of a clear colorless oil which was revealed by ^{1}H NMR to consist of a 3:1 ratio of 5,9-hemiacetal and 9-keto forms: $[\alpha]^{23}_D$ −11.4° (*c* 1.00 $CHCl_3$); IR (neat) 3467, 2974, 2944, 1718, 1456 cm^{-1};^{1}H NMR (400 MHZ, $CDCl_3$) (5,9-hemiacetal form) δ 5.01 (dq, $J = 2.3$, 6.5 Hz, 1H), 4.04 (m, 2H), 3.36 (dd, $J = 1.4$, 10.3 Hz, 1H), 3.33 (d, $J = 2.0$ Hz, 1H), 2.98 (d, $J = 4.6$ Hz, 1H), 2.72 (d, $J = 4.6$ Hz, 1H), 2.55 (dq, $J = <1.0$, 7.1 Hz, 1H), 2.28 (q, $J = 7.0$ Hz, 1H), 2.12 (m, 1H), 1.93 (dd, $J = 12.5$, 14.0 Hz, 1H), 1.69 (m, 2H), 1.43 (dd, $J = 4.2$, 14.0 Hz, 1H), 1.34 (d, $J = 6.5$ Hz, 3H), 1.14 (d, $J = 7.1$ Hz, 3H), 1.03 (d, $J = 7.0$ Hz, 3H), 1.01 (d, $J = 7.4$ Hz, 3H), 0.96 (d, $J = 7.0$ Hz, 3H), 0.85 (d, $J = 6.6$ Hz, 3H); (selected resonances for the 9-keto form) δ 5.67 (dq, $J = 1.2$, 6.7 Hz, 1H), 3.91 (d, $J = 10.9$ Hz, 1H), 3.82 (dd, $J = 1.5$, 10.2 Hz, 1H), 3.07 (d, $J = 4.5$ Hz, 1H), 3.03 (dq, $J = 1.8$, 6.7 Hz, 1H), 2.79 (d, $J = 4.5$ Hz, 1H), 2.73 (dq, $J = 6.7$, 10.1 Hz, 1H), 1.29 (d, $J = 6.7$ Hz, 3H), 1.26 (d, $J = 6.8$ Hz, 3H), 1.09 (d, $J = 6.1$ Hz, 3H), 1.07 (d, $J = 6.9$ Hz, 3H); TLC $R_f = 0.18$ (50% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 409.2202 found 409.2186.

(2*R*,3*S*,4*R*,5*S*,6*S*,8*R*,10*R*,11*S*,12*S*,13*R*)-3,5,11-Triacetoxy-8,8-(epoxymethano)-2,4,6,10,12,13-hexamethyl-9-oxotetradecanolide, Triacetyloleandolide (53). To a solution of 2.6 mg (0.00674 mmol) of triol in 0.5 mL of pyridine were added 0.059 mL of (0.625 mmol) acetic anhydride and a single crystal of *N*,*N*-(dimethylamino)pyridine. The solution was stirred at ambient temperature for 2 d at which time the reaction was concentrated in vacuo and purifed directly by flash chromatography (50% EtOAc/hexanes, 1 × 11 cm SiO_2) to afford a 2.2 mg (64%) of a white powder: $[\alpha]^{23}_D$ +40.6° (*c* 1.00 $CHCl_3$); IR (neat) 2985, 2944, 1728, 1456 cm^{-1};^{1}H NMR (400 MHZ, $CDCl_3$) δ 5.22 (dd, $J = 1.8$, 10.0 Hz, 1H), 5.19 (dq, $J = 1.4$, 6.6 Hz, 1H), 5.00 (dd, $J = 1.8$, 9.8 Hz, 1H), 4.74 (dd, $J = 1.3$, 5.8 Hz, 1H), 3.18 (dq, $J = 1.8$, 6.9 Hz, 1H), 2.75 (dq, $J = 6.9$, 10.1 Hz, 1H), 2.62 (d, $J = 5.7$ Hz, 1H), 2.59 (m, 2H), 2.57 (d, $J = 5.7$ Hz, 1H), 2.31 (m, 1H), 2.08 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.86 (m, 1H), 1.36 (dd, $J = 11.8$, 15.2 Hz, 1H), 1.25 (d, $J = 6.6$ Hz, 3H), 1.07 (m, $J = 6.4$ Hz, 3H), 1.06 (m, $J = 6.8$ Hz, 3H), 1.05 (m, $J = 6.5$ Hz, 3H), 1.01 (m, $J = 7.2$ Hz, 3H), 1.006 (m, $J = 6.7$ Hz, 3H); TLC $R_f = 0.40$ (50% EtOAc/hexanes). HRMS (FAB) *m*/*z* calcd for $[M + Na]^+$ 535.2519 found 535.2523.

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Supporting Information Available: General information, complete procedures, and full characterization data for all compounds including NMR peak assignments and ^{13}C spectra (21 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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